Annals of Medical Research

The Offical Journal of Inonu University Faculty of Medicine

Ann Med Res | Volume: 32 | Issue: 4 | April 2025

Original Articles

Letter to the Editor

Annals of Medical Research

The Offical Journal of Inonu University Faculty of Medicine

Editorial Board | Volume: 32 | Issue: 4 | April 2025

Annals of Medical Research

The Offical Journal of Inonu University Faculty of Medicine

Editorial Advisory Board | Volume: 32 | Issue: 4 | April 2025

Annals of Medical Research

The Offical Journal of Inonu University Faculty of Medicine

Table of Contents | Volume: 32 | Issue: 4 | April 2025

Original Articles

Letter to the Editors

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Does the diagnosis of multiple myeloma show a seasonal difference?

Gulsum Akgun Cagliyan

Pamukkale University, Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Denizli, Türkiye

ARTICLE INFO

Keywords:
Multiple myeloma
Seasonal change
Single center
Diagnosis

Received: Jan 24, 2025
Accepted: Feb 13, 2025
Available Online: 25.04.2025

DOI:
10.5455/annalsmedres.2025.01.029

Abstract

Aim: Multiple myeloma (MM) is a heterogeneous disease caused by genetic and environmental factors. The present study aims to determine whether the diagnosis of MM exhibits a seasonal pattern.

Materials and Methods: Eighty new diagnosed patients with MM between January 2020 and July 2024 were included in the study. All data on gender, age and time of diagnosis were retrospectively analyzed from the files of patients.

Results: Eighty patients newly diagnosed with MM were included in the study. Thirty-four (42.5%) of them were female and 46 (57.5%) were male. The median age of the patients was 63 years (41-81). The month with the highest number of MM diagnoses was November, with nine patients (11.3%), while the month with the least number of diagnoses was July, with four patients (5%). The season with the highest number of diagnoses was winter, with 22 patients (27.5%) diagnosed, followed by spring and autumn, each with 20 patients (25%). The least number of MM diagnoses was observed in the summer, with 18 patients (22.5%). This observation did not reach statistical significance ($p>0.05$). Among the 80 patients, 44 were diagnosed between October and March, while 36 were diagnosed between April and September. The number of new cases was higher in the colder seasons.

Conclusion: In our study, the diagnosis of MM does not appear to show seasonal variation. We observed that new cases with MM increased in the cold months. Since infections are a common presenting feature in Multiple Myeloma (MM), clinicians should maintain a high index of suspicion for MM in patients with recurrent or unusual infections.

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation of monoclonal plasma cells in the bone marrow. These plasma cells originate from post-germinal center B lymphocytes. MM represents approximately 1% of all cancers and is the second most common hematologic malignancy, following lymphoma. The median age at diagnosis is 66-70 years, with approximately 37% of cases occurring in individuals younger than 65. MM is rare in young individuals, particularly those under 30 years old. While familial cases are reported, MM is generally not considered a genetically inherited disease [1-3]. Studies on patients with MM have contributed to a better understanding of the pathophysiology of the disease. Mutations involving chromosome 14 are common in MM and lead to disease development. Mutations involving NRAS (Neuroblastoma RAS viral oncogene homolog), KRAS (Kirsten rat sarcoma viral oncogene homolog), and BRAF (B-Raf proto-oncogene, serine/threonine kinase) play a significant role in the uncontrolled proliferation of plasma cells.

Obesity, alcohol consumption, and exposure to environmental factors such as pesticides, organic solvents, and radiation have been associated with an increased risk of developing MM. The incidence of MM is known to be higher in individuals of Black ethnicity and in males [4,5]. The consumption of fruits, vegetables, whole grains, and seafood has been shown to reduce the risk of MM. MM is also more frequently observed in individuals with vitamin D deficiency [6]. Climate change, environmental pollution, aging, and anemic hypoxia are factors that contribute to an increased risk of MM [7,8]. Environmental and genetic factors play a role in the development of MM. The impact of seasonality on MM diagnosis has not been previously evaluated in Turkey. This study aims to determine whether MM diagnosis exhibits any seasonal variation.

*Corresponding author:
Email address: drgulsumakgun@gmail.com (Gulsum Akgun Cagliyan)

Materials and Methods

We included 80 newly diagnosed patients with MM between January 2020 and July 2024. All patients underwent routine tests necessary for the diagnosis of MM, including complete blood count, biochemistry, sedimentation rate, immunoglobulins, free light chains, serum and 24-hour urine protein electrophoresis and immunofixation, as well as bone marrow aspiration and biopsy. Data regarding the age, gender, time of diagnosis, stage, and MM subtype for all the patients were retrospectively collected from the medical records. Renal involvement was defined as acute renal injury, chronic renal injury, proteinuria, hematuria, renal crystallopathy, and hypercalcemia.

Written informed consent was obtained from all patients, and the study was conducted under the principles of the Helsinki Declaration.

Statistical analysis

Statistical analyses were performed using Statistical software Package for Social Sciences (SPSS) for Windows version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Categorical data were presented as frequencies and percentages, while continuous variables were summarized as mean ± standard deviation or median (min-max) based on their distribution. The study utilized a non-probability convenience sampling method. The sample size was calculated using a population proportion formula with a 95% confidence level, a margin of error of 5%, and an assumed prevalence of seasonal variation in diagnoses of hematologic malignancies based on the literature data. Based on these parameters, a minimum sample size of 73 was determined. To account for potential data inconsistencies, 80 patients newly diagnosed with multiple myeloma between January 2020 and July 2024 were included in the study.

Results

The study included 80 newly diagnosed patients with multiple myeloma (MM), comprising 34 females (42.5%) and 46 males (57.5%). The median age of the patients was 63 years, ranging from 41 to 81 years. The median hemoglobin level was 9.8 g/dl, with values ranging from 5.5 to 15.8 g/dl. The median sedimentation rate was 88 mm/h, ranging from 28 to 159 mm/h. According to the Revised International Staging System (R-ISS), 14 patients (17.5%) were classified as stage I, 28 patients (35%) were classified as stage II, and 38 patients (47.5%) were classified as stage III. Renal involvement at diagnosis was observed in 33 patients (41.3%). The most common type of MM was IgG Kappa. The characteristics of the patients are presented in Table 1.

Table 1. Characteristics of Patients with Multiple Myeloma.

	n=80
Age (median, min-max)	63 (41-81)
Gender	
Female	34 (42.5 %)
Male	46 (57.5 %)
Leukocytes (mm^3) (median, min-max)	6520 (2540-15540)
Hemoglobin (gr/dl) (median,min-max)gr/dl	9.8 (5.5-15.8)
Platelets (mm^3) (median, min-max)	215.000 (16.000-551.000)
Sedimentation (mm/h)	88 (28-159)
B2 microglobulin (mg/L)	7.06 (2.01-20.4)
Stage (R-ISS) (I,II,III)	14 (17.5%), 28 (%35%), 38(47.5%)
Presence of renal involvement	33 (41.3%)
MM type	
Ig G Kappa	45 (56.25%)
Ig G Lambda	22 (27.5%)
Ig A Kappa	6 (7.5%)
Ig A Lambda	4 (5%)
Nonsecretory	3 (3.75%)

Table 2. Distribution of Patients Diagnosed with Multiple Myeloma According to Months and Seasons.

Months	n=80	Seasons	n=80
December	7 (8.8%)		
January	7 (8.8%)	Winter	22 (27.5 %)
February	8 (10%)		
March	8 (10%)		
April	7 (8.8%)	Spring	20 (25 %)
May	5 (6.3%)		
June	7 (8.8%)		
July	4 (5%)	Summer	18 (22.5 %)
August	7 (8.8%)		
September	6 (7.5%)		
October	5 (6.3%)	Autumn	20 (25 %)
November	9 (11.3%)		

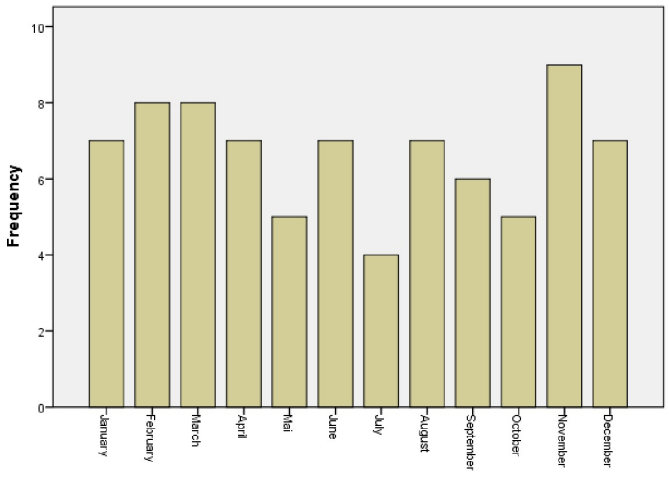

Figure 1. Monthly Distribution of newly diagnosed patients with MM.

The distribution of MM diagnoses by month is illustrated in Figure 1, and the monthly and seasonal distribution of diagnoses is detailed in Table 2. November had the highest number of MM diagnoses with 9 patients (11.3%), whereas July had the fewest diagnoses with 4 patients (5%). Winter recorded the highest number of diagnoses with 22 pa-

tients (27.5%), followed by spring and autumn, each with 20 patients (25%). Summer had the lowest number of MM diagnoses with 18 patients (22.5%). An evaluation of newly diagnosed MM patients based on the season of diagnosis revealed no significant difference ($p>0.05$) (Table 2). Furthermore, 44 patients were diagnosed between October and March, while 36 patients were diagnosed between April and September, indicating a higher number of diagnoses during colder seasons.

Discussion

Multiple Myeloma (MM) is an incurable disease characterized by relapses despite improved survival and response rates with proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibody treatments [9,10]. As our understanding of the tumor microenvironment and genetic landscape deepens, the pathogenesis and treatment response risk factors for MM will become clearer. MM is a heterogeneous disease, and the impact of seasonality on MM remains uncertain. This study aims to present single-center analysis data to determine if a seasonal variation in MM exists.

Several studies have evaluated seasonality in hematologic malignancies. Factors such as aging, air pollution, dry seasons, and global warming have been identified as significant determinants of hematologic malignancies among African patients [11]. Hassan et al. [12] assessed 1982 cases of hematologic diseases over a 10-year period. They observed a seasonal relationship with acute leukemia, aplastic anemia, and immune thrombocytopenia, with an increased number of cases during the southwest monsoon period. However, no specific seasonal relationship was found with acute promyelocytic leukemia. Borchmann et al. [13] conducted a study involving 41,405 cases of Hodgkin lymphoma and identified a seasonal relationship, suggesting a protective role for vitamin D in Hodgkin lymphoma.

Data from Atlanta, evaluating seasonality in 120 MM patients, showed significant seasonal variation in MM frequency. Over five years, an average of 10 cases were diagnosed per month. From October to March, monthly diagnoses exceeded 10, while from April to September, they were 10 or fewer. In total, 77 cases were diagnosed between October and March, whereas only 43 cases were diagnosed between April and September. When correlating these data with Atlanta's average monthly temperatures, an increase in MM diagnoses during colder months was observed. However, this correlation was deemed inconclusive. For instance, April, with only five diagnoses, was on average two degrees colder than October, which had 14 diagnoses. While the winter predominance in the entire cohort cannot be fully explained, it suggests that acute respiratory infections may accelerate MM diagnosis [14]. In the present study, 44 of the 80 patients were diagnosed between October and March, while 36 were diagnosed between April and September. Specifically, 22 cases were diagnosed during winter, 20 each in spring and autumn, and 18 during summer. November had the highest number of diagnoses (9 cases), while July had the fewest (4 cases). More cases were observed during the colder months.

MM is characterized by bone involvement, renal failure, anemia and cytopenias, elevated sedimentation rate, hypercalcemia, coagulation abnormalities, neurological symptoms, hyperviscosity, and increased susceptibility to infections [4,5]. Infections are frequently observed in MM patients due to age-related immune dysfunction, changes in immunoglobulin production, and treatment-related immunosuppression. The risk of opportunistic bacterial and viral infections, including seasonal influenza viruses, increases by 7-10 times in MM patients. Deaths in MM often result from disease progression or infections [5,6]. Patients presenting with infection-related symptoms facilitate the diagnosis of MM. Both the Atlanta data and the present study have shown increased MM diagnoses during periods of heightened respiratory tract infections.

Climate change, excessive ultraviolet radiation exposure, and vitamin D deficiency contribute to immune system impairment in MM. A study at the Mayo Clinic evaluated vitamin D deficiency in 148 newly diagnosed MM patients and found no seasonal variation in vitamin D status. Given that vitamin D levels can be significantly influenced by skin pigmentation, sun exposure, geographic location, and diet, the lack of a seasonal correlation is understandable [15]. Vitamin D levels were not evaluated in the present study, which is a limitation to be considered.

Conclusion

Our study found no seasonal variation in the diagnosis of multiple myeloma (MM). However, there was an increase in new MM cases during the colder months, specifically with patients presenting infection findings, leading to faster diagnoses. MM is a hematologic malignancy associated with higher morbidity and mortality. Understanding the factors that increase susceptibility to MM requires prioritizing improvements in lifestyle habits, diagnostic capacity, and treatment availability. Future research should investigate the underlying causes of these trends.

Disclosures

Ethics Committee Approval: We performed our study with the approval of the institutional review board (Date: 23.07.2024; Decision Number: E-60116787-020-556369).

Informed Consent: Not necessary for this manuscript.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflicts of interest to declare.

References

1. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. *Semin Oncol.* 2016 Dec;43(6):676-681. doi: 10.1053/j.seminoncol.2016.11.004.
2. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med.* 2011 Mar 17;364(11):1046-60. doi: 10.1056/NEJMra1011442.
3. Kyle RA, Gertz MA, Witzig TE,et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.* 2003 Jan;78(1):21-33. doi: 10.4065/78.1.21.
4. Kiss S, Gede N, Soós A, et al. Efficacy of first-line treatment options in transplant-ineligible multiple myeloma: A network meta-analysis. *Crit Rev Oncol Hematol.* 2021 Dec;168:103504. doi: 10.1016/j.critrevonc.2021.103504.
5. Herget GW, Kälberer F, Ihorst G, et al. Interdisciplinary approach to multiple myeloma - time to diagnosis and warning signs. *Leuk Lymphoma.* 2021 Apr;62(4):891-898. doi: 10.1080/10428194.2020.1849681.

6. Gressens SB, Enouf V, Créon A,et al. Serological responses against seasonal influenza viruses in patients with multiple myeloma treated or untreated with daratumumab after two doses of tetravalent vaccine. *Int J Infect Dis.* 2024 Sep;146:107108. doi: 10.1016/j.ijid.2024.107108.
7. Kiss S, Gede N, Soós A, et al. Efficacy of first-line treatment options in transplant-ineligible multiple myeloma: A network meta-analysis. *Crit Rev Oncol Hematol.* 2021 Dec;168:103504. doi: 10.1016/j.critrevonc.2021.103504.
8. Shah UA, Parikh R, Castro F, et al. Dietary and microbiome evidence in multiple myeloma and other plasma cell disorders. *Leukemia.* 2023 May;37(5):964-980. doi: 10.1038/s41375-023-01874-4.
9. Rodriguez-Otero P, Paiva B, San-Miguel JF. Roadmap to cure multiple myeloma. *Cancer Treat Rev.* 2021 Nov;100:102284. doi: 10.1016/j.ctrv.2021.102284.
10. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *Am J Hematol.* 2020 May;95(5):548-567. doi: 10.1002/ajh.25791.
11. Nkanga MSN, Longo-Mbenza B, Adeniyi OV, et al. Ageing, exposure to pollution, and interactions between climate change and local seasons as oxidant conditions predicting incident hematologic malignancy at KINSHASA University clinics, Democratic Republic of CONGO (DRC). *BMC Cancer.* 2017 Aug 23;17(1):559. doi: 10.1186/s12885-017-3547-3.
12. Hassan J, Adil SO, Haider Z, Zaheer S, Anwar N, Nadeem M, Ansari SH, Shamsi T. Seasonal variations in hematological disorders: A 10-year single-center experience. *Int J Lab Hematol.* 2021 Feb;43(1):93-98. doi: 10.1111/ijlh.13337.
13. Borchmann S, Müller H, Engert A. Hodgkin Lymphoma has a seasonal pattern of incidence and mortality that depends on latitude. *Sci Rep.* 2017 Nov 2;7(1):14903. doi: 10.1038/s41598-017-14805-y.
14. McPhedran P, Heath CW Jr, Garcia J. Multiple myeloma incidence in metropolitan Atlanta, Georgia: racial and seasonal variations. *Blood.* 1972 Jun;39(6):866-73.
15. Ng AC, Kumar SK, Rajkumar SV, et al. Impact of vitamin D deficiency on the clinical presentation and prognosis of patients with newly diagnosed multiple myeloma. *Am J Hematol.* 2009 Jul;84(7):397-400. doi: 10.1002/ajh.21412.

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Analysis of newborn hearing screenings from 2018-2022

Ahmet Aksoy[a,*], Baris Sapci[a], Melek Kekul Sapci[b]

[a] *Cumhuriyet University, Faculty of Medicine, Department of Otorhinolaryngology, Sivas, Türkiye*
[b] *Cumhuriyet University, Faculty of Medicine, Education and Research Hospital Audiology Unit, Sivas, Türkiye*

ARTICLE INFO

Keywords:
Auditory brainstem response
Otoacoustic emission
Congenital hearing loss
Hearing screening

Received: Jan 14, 2025
Accepted: Mar 07, 2025
Available Online: 25.04.2025

DOI:
10.5455/annalsmedres.2025.01.017

Abstract

Aim: This study aims to assess the Newborn Hearing Screening (NHS) program conducted in Sivas province between 2018 and 2022. The main objectives include determining the percentage of infants who failed the screening, investigating potential reasons, and outlining the follow-up and treatment procedures for infants diagnosed with congenital hearing loss.

Materials and Methods: This study analyzed the outcomes of otoacoustic emissions (OAE) and screening Auditory Brainstem Response (ABR) in infants undergoing newborn hearing screening. We analyzed the prevalence of congenital hearing loss and identified associated risk factors in affected infants. It also documented the types and rates of treatments administered to infants diagnosed with hereditary hearing loss.

Results: Of 6,585 babies, 27.12% failed the first hearing screening, and 15.5% failed the subsequent screening. During the second screening, 45 babies failed the tests and underwent clinical Auditory Brainstem Response (ABR) testing. We detected congenital hearing loss in 45 infants. Among these,23 infants were fitted with hearing aids, 12 underwent cochlear implantation, and 10 followed up. As a result, the rate of congenital hearing loss in infants was 0.68%.

Conclusion: Recent 5-year data on newborn hearing screening shows congenital hearing loss of 0.48% for bilateral hearing loss and 0.68% for total hearing loss, aligning with existing literature. Screening initiatives are crucial in identifying hearing loss early and integrating individuals into society through interventions that restore hearing functions while preserving cognitive development.

Introduction

A deficiency in hearing results in defects in language, speech, adaptability, and communication skills. The absence of normal hearing in the neonatal period can profoundly affect speech, language development, and cognitive, social, and emotional growth [1]. Congenital hearing loss affects around 1 in 1000 live births, with a higher frequency in high-risk groups [2,3]. Newborns may be at risk of hearing loss due to various factors. These include premature birth (gestational age ≤34 weeks), low birth weight (<1500 g), being born to deaf parents, TORCH infections, neurological disorders, hyperbilirubinemia, craniofacial anomalies, known syndromes associated with hearing loss, and severe birth asphyxia (APGAR score below seven at 5 minutes). Around 3-5% of newborns were reported to be at risk of permanent hearing loss [3].

Every year, over 500,000 babies are born with significant hearing loss. Delayed diagnosis can negatively impact their language and speech skills, and this can have an adverse effect on their academic progress [4]. A child with moderate hearing loss who does not use auditory amplification may miss up to 50% of daily conversations [5]. Early diagnosis of hearing loss in newborns is crucial because the best treatment outcomes are obtained within the first three months after birth. Early intervention before the baby reaches six months old is advisable if hearing loss is detected. It is not uncommon for families to overlook profound hearing loss in infants during their early years, while mild or moderate hearing loss may not be noticeable until the child reaches school age. Surveillance tests for hearing have been implemented to help identify hearing impairments early on [6]. The United States and other Western countries introduced newborn hearing surveillance programs in the late 1990s. Marmara University began implementing these programs in Turkey in 1996, initially at the hospital level. The first official protocol was signed in 2004 and became mandatory nationwide in 2007 [5,7]. Sivas State Hospital initiated hearing screenings in 2007,

*Corresponding author:
Email address: ahmetaksoy@cumhuriyet.edu.tr (Ahmet Aksoy)

and from May 2010 onwards, Sivas Cumhuriyet University actively conducted screenings.

The initial hearing screening tests for infants include Transient Evoked Otoacoustic Emissions (TEOAE) and screening Auditory Brainstem Response (ABR). If a baby fails these tests twice, it will undergo clinical ABR testing to determine if it has congenital hearing loss. If a diagnosis confirms hearing loss, hearing aids should be recommended. Cochlear or brainstem implants are suggested for infants without hearing aids [5,7].

We aimed to analyze the Newborn Hearing Screening (NBST) programs conducted in Sivas province between 2018 and 2022, determine the proportion of infants who failed screening, and reveal the predisposing factors that may contribute to this outcome. It also aims to present the follow-up and treatment procedures for infants diagnosed with congenital hearing loss.

Materials and Methods

Following the approval of the institutional review board for scientific ethical conduct (2023-06/26) and the Ethics Committee of Sivas Provincial Health Directorate (2023/24), a retrospective evaluation of the hearing screening results was conducted for infants referred to our clinic, serving as the reference center for Newborn Hearing Screening (NHS), between 2018 and 2022. This research included infants admitted to the neonatal intensive care unit from other hospitals within or outside the city and those born in our hospital and undergoing hearing screening. A certified nurse conducted the hearing screenings, and at the reference center, two audiometry technicians and two audiologists performed the audiology tests. Before February 2019, the newborn screening test involved TEOAE. The test serenely took place with the baby in a natural sleep and well-fed state in a quiet and calm environment, either in the mother's arms or on a flat surface.

The sample size of this study was determined retrospectively based on the total number of infants who underwent the Newborn Hearing Screening (NHS) program at our reference center between 2018 and 2022. A total of 6,585 newborns were screened during this period. No separate sample size calculation was required since all eligible newborns within the specified timeframe were included. Instead, a complete enumeration sampling method was employed, meaning that every infant who met the inclusion criteria was included in the study. This methodology eliminates potential sampling bias and enhances the generalizability of the findings.

As this study includes all infants who underwent screening at the reference center within the specified period, it did not utilize a probabilistic or non-probabilistic sampling approach but followed a census-based methodology. The study ensured a robust dataset free from selection bias by incorporating the entire screened population. It provided findings that accurately represent the outcomes of neonatal hearing screening in the region.

The Maico ERO Scan analyzer (GmbH Salzufer, 13/14, 10587, Berlin, Germany) conducted the TEOAE test. We selected the probes based on the baby's external ear canal size. The test results displayed "PASS" on the screen for ears that responded and "REFER" for those that did not. The screening test was successful if it automatically detected a "PASS" result. We utilized the TEOAE test to take bilateral measurements during hearing screenings. If we could not obtain a unilateral or bilateral emission response, we duly informed the families of the infants and requested that they undergo a retest after 15 days. During subsequent appointments, infants who did not pass the unilateral or bilateral TEOAE test underwent an examination to determine any potential influences on the test results. This examination involved an assessment of factors such as middle ear effusion and external ear canal pathologies through an otoscopic examination. After conducting this evaluation, we retested the infants.

In cases where the TEOAE test did not yield successful results in the initial two follow-ups, we recommended that individuals seek additional screening at our reference center. Our comprehensive screening procedure involved an ABR evaluation, administered with the aid of the GN Otometrics ICS Chartr EP 200 device from Denmark. The result of this assessment is defined as a "pass" or "fail." In writing, we communicated screening results to families and recorded the data in follow-up forms. Various parameters, including the gender of screened infants, birth weight, delivery method, neonatal unit stay, gestational age, place of birth (our university or referred location), TEOAE test results, and other records, such as ABR, were evaluated if available. Since February 2019, ABR has been used to assess hearing functions. Measurement was conducted using the MB 11 BERAphone Maico® device within 72 hours after birth, before the mother and baby were discharged. The reference value for the measurement was set at 35 dB nHL. A response at 35 dB nHL was considered a "PASS" when confirmed during the test. In cases where no response was obtained or could not be established, the test result was recorded as "REFER." The screening process utilized a "PASS" outcome as the success benchmark, with measurements conducted in both ears in sequence. If the result was unsuccessful, they scheduled a follow-up appointment after 14 days. Before the second test, an ear examination was performed to evaluate potential issues with the middle ear or external ear canal that could impact the results. Infants who did not pass the second test were referred to our reference center for further assessment due to suspected hearing loss.

Inclusion criteria for this study consisted of all newborns who underwent the Newborn Hearing Screening (NHS) program at our reference center between 2018 and 2022, regardless of their risk status. Both infants born in our hospital and those referred from external hospitals were included, provided they completed at least one stage of the screening process.

Exclusion criteria included infants who did not undergo any NHS testing, those with incomplete medical records preventing verification of hearing test results, and those whose parents declined participation in follow-up assessments. Infants lost to follow-up were recorded separately and not included in the final prevalence and statistical analyses dataset. However, their numbers are documented for transparency.

Newborns referred from external hospitals were managed

following the same standardized screening protocol as those born in our hospital. All infants, regardless of birthplace, underwent otoacoustic emissions (OAE) screening as a first step. If an infant failed the initial screening, a second test was performed within 15 days. Infants who failed the second screening were referred for clinical Auditory Brainstem Response (ABR) testing at our reference center.

To minimize potential selection bias, the data from referred infants were analyzed separately for comparative purposes. However, due to the standardized testing and follow-up protocol applied across all cases, significant procedural differences were not observed.

The study aimed to determine the percentage of infants who failed either TEOAE or screening ABR tests during the NHS and later underwent clinical ABR testing. The study also investigated the types and degrees of hearing loss among infants who underwent clinical ABR. Furthermore, the study determined the percentage of congenital hearing loss and identified risk factors for infants with recognized hearing loss. We reported the types and rates of treatments administered to infants with hereditary hearing loss.

Statistical analysis

Statistical analyses were conducted using Statistical Software Package for Social Science for Windows, version 22.0 (SPSS v22) (IBM Corp., Armonk, NY, USA, Licensed Software). As the study included only categorical variables, descriptive statistics were presented as frequencies and percentages (n, %). A chi-square test was used to examine the relationships between categorical variables. The Fisher-Freeman-Halton Exact Test was used when the assumption of expected cell frequencies greater than five was unmet. A p-value less than 0.05 was considered statistically significant.

Results

Between 2018 and 2022, 4,799 infants (72.88%) successfully passed the first hearing screening, whereas 1,786 infants (27.12%) required further evaluation. In the second screening, 1,509 infants (84.5%) passed, while 277 infants (15.5%) remained in the screening process. Infants who did not pass the second screening underwent clinical Auditory Brainstem Response (ABR) testing, where 232 infants were identified as having normal hearing, and 45 infants were diagnosed with congenital hearing loss. The flow chart of the patients is summarized in Figure 1.

Table 1. Treatment Modalities used in infants with congenital hearing loss, n(%).

Types of Treatment	Infants with Congenital Hearing Loss
Hearing aid rehabilitation	23(51.1)
Cochlear implant	12(26.7)
Follow-up	10(22.2)
p*	**0.038**

*: Chi-Square Test.

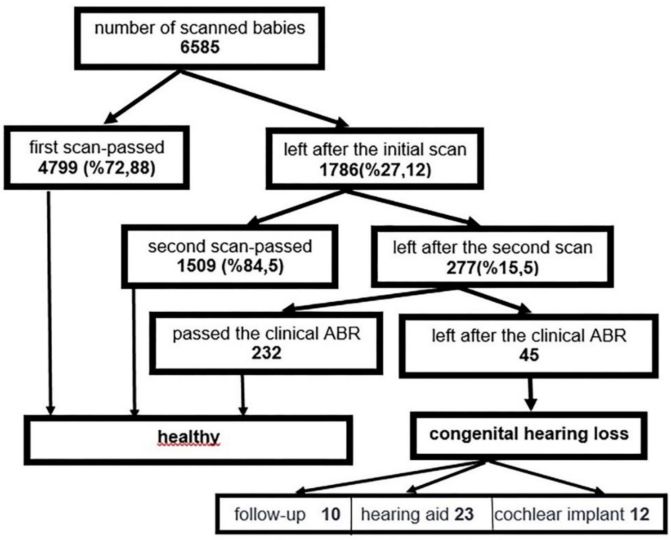

Figure 1. Results of newborn hearing screenings, [6192 screening ABR, 391 screening OAE, 45/6585=percentage of congenital hearing loss (%0.68)].

The study evaluated the 45 infants diagnosed with congenital hearing loss in depth. Thirty-one (68.9%) were male, and 14 (31.1%) were female. The analysis of treatment modalities applied in infants with congenital hearing loss revealed that hearing aid rehabilitation was the most frequently utilized method, accounting for 51.1% (n = 23) of cases (Table 1). Cochlear implantation was performed in 26.7% (n = 12) of the infants, while 22.2% (n = 10) were placed under follow-up without immediate intervention.

A chi-square test indicated a statistically significant difference in the distribution of treatment modalities; hearing aid was the most frequent treatment modality among the study group (p = 0.038). This finding suggests that selecting treatment methods is not random and may be influenced by specific clinical criteria, such as the severity of hearing loss, anatomical suitability for cochlear implantation, or other patient-related factors.

The distribution of the risk factors for congenital hearing loss between male and female infants is summarized in Table 2. Statistical analyses revealed no significant associations between congenital hearing loss risk factors and gender (p=1.000). Specifically, no significant differences were observed in prematurity, low birth weight (<1500 g), history of intensive care (≥5 days), family history of hereditary hearing loss, or craniofacial anomalies between male and female infants. These findings suggest that gender is not a determining factor in developing congenital hearing loss.

The relationship between treatment methods and gender was not statistically significant (p = 0.911) (Table 3). This finding suggests that gender is not a determining factor in selecting treatment methods. Similarly, no statistically significant association was observed between birth weight categories and the applied treatment methods (p = 0.450). Furthermore, the relationship between gestational age and treatment methods was not statistically significant (p = 0.681). Additionally, no significant association was found between the four prematurity classifications based on gestational age and the treatment methods administered (p =

Table 2. Risk factors for hearing in newborns according to gender, n(%).

Risk Factors for Infants with Congenital Hearing Loss	Male	Female	p
Premature	5(15.6)	1(20.0)	1.000[&]
Birth weight less than 1500 g	5(15.6)	1(20.0)	
Hyperbilirubinemia	0(0.0)	0(0.0)	
History of intensive care unit stay (more than five days)	9(28.9)	1(20.0)	
History of phototherapy	0(0.0)	0(0.0)	
Consanguineous marriage of parents	0(0.0)	0(0.0)	
Family history of hereditary hearing loss	7(21.9)	1(20.0)	
Craniofacial anomaly	5(15.6)	1(20.0)	
History of bacterial meningitis	0(0.0)	0(0.0)	
History of Ototoxic Drugs	0(0.0)	0(0.0)	
Apgar scores below four at 5 minutes	0(0.0)	0(0.0)	
The child with syndromic features along with congenital hearing loss	1(3.1)	0(0.0)	

[&]: Fisher Freeman Halton Exact Test.

Table 3. Treatment methods.

Variables	Hearing Aid	Implant	Follow-up	p
Gender, n(%)				
Male	15(65.2)	9(75.0%)	7(70.0)	0.911[&]
Female	8(34.8%)	3(25.0%)	3(30.0)	
Birth weight, n(%)				
Normal delivery	18(85.7)	6(60.0)	8(88.9)	
<1000 g	0(0.0)	1(10.0)	0(0.0)	0.450[&]
1000 -1500 g	1(4.8)	0(0.0)	0(0.0)	
1500 -2500 g	2(9.5)	2(20.0)	1(11.1)	
Over 4000 g	0(0.0)	1(10.0)	0(0.0)	
Birth week, n(%)				
Miad	17(73.9)	9(75.0%)	6(60.0%)	0.681[&]
Preterm	6(26.1)	3(25.0%)	4(40.0%)	
Gestational age, n(%)				
Term (38-42 weeks)	17(73.9)	9(75.0)	6(60.0%)	
Preterm (36-37 weeks)	3(13.0)	0(0.0)	4(40.0%)	0.193[&]
Moderate preterm (32-35 weeks)	1(4.3)	1(8.3)	0(0.0)	
Extremely preterm (24-31 weeks)	2(8.7)	2(16.7)	0(0.0)	

&: Fisher Freeman Halton Exact Test.

Table 4. Distribution of risk conditions in infants with congenital hearing loss, n(%).

Risk Factors for Congenital Hearing Loss in Infants	Number of Infants
No risk	21(46.7)
Intensive care unit stay for more than 5 days	3(6.7)
Family history of hearing loss	6(13.3)
Presence of Craniofacial anomalies involving the middle ear and need for intensive care unit stay for more than 5 days.	2(4.4)
Earlobe anomalies, ear canal anomalies, family history of hearing loss	5(11.1)
Earlobe anomalies	1 (2.2)
Prematurity, low birth weight, and need for intensive care unit stay for more than 5 days.	6(13.3)
Maternal diseases during pregnancy (hypothyroidism, hypertension, and gestational diabetes)	1(2.2%)
p*	**0.000**

*: Chi-Square Test.

0.193). These results indicate that factors such as preterm birth or low birth weight do not have a decisive impact on treatment selection.

This study examined the distribution of risk factors in infants with congenital hearing loss (Table 4). Among the 45 infants included in the analysis, 21 (46.7%) had no identified risk factors. However, various risk factors were detected, including a history of intensive care stay exceeding five days (6.7%), a family history of hearing loss (13.3%), and middle ear and craniofacial anomalies combined with

Table 5. Risk factors of the study group.

Variables	No Risk	Prolonged ICU stay >5 days	Hearing loss in family	Craniofacial Anomalies, Prolonged ICU Stay >5 days	Ear Anomalies, Family History of Hearing Loss	Anomalies of the auricle	Prematurity, Low Birth Weight, Prolonged ICU Stay >5 days	Pregnancy-related maternal diseases	p
Gender, n(%)									
Male	11(52.4)	3(100.0)	5(83.3)	2(100.0)	4(80.0)	1(100.0%)	5(83.3)	0(0.0)	0.352&
Female	10(47.6)	0(0.0)	1(16.7)	0(0.0)	1(20.0)	0(0.0%)	1(16.7)	1(100.0)	
Birth weight, n(%)									
Normal birth	17(94.4)	3(100.0)	4(80.0)	2(100.0)	5(100.0)	1(100.0)	0(0.0)		
<1000 g	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	
1000 -1500 g	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	**0.002**&
1500 -2500 g	1(5.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(66.7)	0(0.0)	
Over 4000 g	0(0.0)	0(0.0)		0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	
Birth week, n(%)									
Miad	17(81.0)	2(66.7)	5(83.3)	2(100.0)	5(100.0)	1(100.0)	0(0.0)	0(0.0)	**0.001**&
Preterm	4(19.0)	1(33.3)	1(16.7)	0(0.0)	0(0.0)	0(0.0)	6(100.0)	1(100.0)	
Gestational age, n(%)									
Term (38-42 weeks)	17(81.0)	2(66.7)	5(83.3)	2(100.0)	5(100.0)	1(100.0)	0(0.0)	0(0.0)	
Preterm (36-37 weeks)	4(19.0)	1(33.3)	1(16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	**0.001**&
Moderate preterm (32-35 weeks)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(33.3)	0(0.0)	
Extremely preterm (24-31 weeks)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(66.7)	0(0.0)	

&: Fisher Freeman Halton Exact Test, ICU; Intensive Care Unit.

a prolonged intensive care stay (4.4%).

Additionally, a combination of earlobe anomalies and a family history of hearing loss was observed in 11.1% of cases. Prematurity, low birth weight, and prolonged intensive care admission were collectively identified in 13.3% of the infants. The presence of maternal diseases during pregnancy, such as hypothyroidism, hypertension, and gestational diabetes, was noted in 2.2% of cases.

A chi-square test revealed a statistically significant difference in the distribution of risk factors ($p = 0.000$).

The relationship between various demographic and perinatal characteristics and the presence of risk factors for congenital hearing loss was analyzed (Table 5). The absence of risk factors was more frequently observed in male infants (52.4%) than in females (47.6%), but this difference was not statistically significant ($p = 0.352$).

Birth weight was significantly associated with risk factors ($p = 0.002$). Infants with normal birth weight (2500–4000 g) had the highest proportion of cases without identified risk factors (44.4%). In contrast, all infants with extremely low birth weight (<1000 g) and very low birth weight (1000–1500 g) had at least one risk factor, with some requiring prolonged intensive care stays. Additionally, infants with birth weight over 4000 g exhibited a higher prevalence of risk factors such as prematurity and intensive care admission.

Gestational age at birth was also significantly related to the presence of risk factors ($p = 0.001$). Full-term infants ($\geq$38 weeks) had the highest proportion of cases without risk factors (81%), whereas preterm infants, particularly those born at $\leq$31 weeks, showed an increased likelihood of risk factors, including prolonged intensive care stays and prematurity-related complications. Notably, all infants born at 24–31 weeks exhibited at least one risk factor, with 66.7% requiring intensive care for more than five days.

Additionally, maternal diseases during pregnancy, including hypothyroidism, hypertension, and gestational diabetes, were more prevalent in preterm births, particularly among infants requiring neonatal intensive care. The association between maternal diseases and risk factors for congenital hearing loss approached statistical significance ($p = 0.06$).

Discussion

Delayed diagnosis and treatment of congenital hearing loss have been shown to negatively impact the speech functions of infants, resulting in delayed language development and affecting their cognitive and behavioral growth [1,4,5]. It is crucial to prioritize the timely diagnosis and treatment of congenital hearing loss to mitigate the potential adverse outcomes and optimize the overall development of the infants. The American Academy of Pediatrics has recommended that infants be screened for hearing before three months and initiate any necessary treatment before six months of age in individuals with abnormal hearing tests [1-4].

Advanced objective tests are employed to evaluate hearing functions in infants during screenings. Two commonly used methods are Otoacoustic Emissions (OAE) and ABR screening. The OAE device, developed by David Kemp in 1978, evaluates the portion of the auditory pathway up to the outer hair cells in the cochlea. In contrast, the auditory pathways from the cochlear nerve to the brainstem are assessed through stimulus in the auditory brainstem. Otoacoustic emissions are an objective measurement based on recording waves generated in the cochlea in response to sound stimuli. However, debris in the ear canal, earwax, or inflammation in the middle ear can adversely affect OAE measurements. Screening ABR can be conducted more quickly; however, clinical ABR demands more time and technical expertise [1,4]. OAE and ABR tests are commonly used to evaluate different hearing domains.

Maris et al. [8] conducted a retrospective analysis on infants who failed the newborn hearing screening. They concluded that ABR should be the preferred method for newborn hearing screening due to its higher prevalence in detecting auditory neuropathy/dysynchrony [8]. The congenital hearing loss rate is reported to be between 0.1% and 0.6% [2,6].

We found the rate of congenital hearing loss in our region to be close to the literature, being 0.68%, with a bilateral rate of 0.48%. Ohl et al. [3] determined the rate of permanent hearing loss to be 3-5% and attributed this high rate to the presence of high-risk groups [3]. Genç et al. [5]reported that 0.2% of the 5485 infants had bilateral severe hearing loss. A large-scale study conducted in Japan reported a prevalence of congenital hearing loss at 1.62 per 1,000 newborns (0.162%), with bilateral cases accounting for 0.84 per 1,000 (0.084%) and unilateral cases at 0.77 per 1,000 (0.077%). Notably, these rates are lower than those in our study [9]. A systematic review of European neonatal hearing screening programs reported a prevalence of bilateral hearing loss ranging from 0.5 to 20.94 per 1,000 newborns. Most screening programmes achieved coverage rates exceeding 90% [10]. Between July 2018 and September 2020, 7,287 neonates in China were screened for hearing loss, revealing a prevalence of 3.43 per 1,000 (0.343%). Of the 25 confirmed cases, 68% (17 cases) had bilateral hearing loss (0.23% of all neonates), while 32% (8 cases) had unilateral hearing loss (0.11% of all neonates) [11]. The estimated prevalence of permanent bilateral hearing loss is 1.33 per 1,000 live births in regions with universal newborn hearing screening programs. In contrast, areas without such programs have higher prevalence rates, with 19 per 1,000 in sub-Saharan Africa and 24 per 1,000 in South Asia [12]. The observed variations in prevalence rates among the studies may be attributed to differences in study design, screening protocols, diagnostic criteria, population demographics, and healthcare infrastructure across regions.

The presence of risk factors for hearing functions in infants increases the rate of congenital hearing loss. Ototoxic medication, prematurity, low birth weight, and staying in the intensive care unit for more than seven days are reported as significant risk factors [6]. Acar et al. [2] investigated the risk factors in newborns with congenital hearing loss. They identified mechanical ventilation, family history of hearing loss, and consanguineous marriage as the most important risk factors [2].

In infants with congenital hearing loss, we observed that the most important risk factors were a family history of hearing loss, low birth weight, prematurity, and staying in the intensive care unit for more than five days. Sabbagh et al. [13] reported that premature babies (<35 weeks) had an increased risk of sepsis due to a weaker immune system, making them more susceptible to various infections and increased the risk of hearing loss. Additionally, they reported that ototoxic drugs, gestational diabetes, seizures, hyperbilirubinemia, low birth weight, consanguineous marriage, family history of hearing loss, staying in the intensive care unit for more than five days, and craniofacial anomalies further increased the rate of congenital hearing loss [7,13-16]. A study from Beijing found that 55.7% of newborns referred from hearing screening had confirmed hearing loss, highlighting the impact of comprehensive screening and risk factors such as craniofacial anomalies and low birth weight [17]. Karaca et al. [4] added that vaginal delivery and infections during pregnancy were additional risk factors for newborn hearing loss [4].

Throughout the history of hearing screening protocols, studies were initiated as school screenings and eventually extended to early periods of life. Kemaloğlu et al. [18] conducted a study on hearing screening, reporting that approximately 88% of newborns underwent NHS testing in 2013. They stressed the need for an extra hearing screening program for children in developing nations like Turkey to address factors such as infections, trauma, and ototoxicity [18]. The national hearing screening program estimates that screening can be performed in 95% of newborns, and the objective is to increase this rate [19].

Authorities report a hearing screening test conduct rate between 96-98% in Sivas province. It is crucial for infants diagnosed with hearing loss to undergo hearing rehabilitation before the age of 6 months. Eligible cases should receive hearing aids. Similarly, for infants who do not benefit from hearing aids, timely implant surgery (cochlear or brainstem implant) is necessary to enhance the child's cognitive, behavioral, and hearing functions more efficiently [2]. Among the patients, 23 received hearing aids, 12 underwent cochlear implantation, and the remaining were followed up.

Rockwell et al. [20] found that 16.2% of infants monitored in their institutions could not receive proper monitoring during the pandemic. Another research study conducted in the Maryland region of the United States reported that around one-third of infants who failed their hearing screenings in 2020 and an estimated three-fourths of those who failed in 2021 did not complete their follow-up hearing screenings or seek any follow-up care after being referred for a newborn hearing screening. The researchers emphasized that hearing screening programs across the United States were disrupted in many institutions during the COVID-19 pandemic [20,21].

The COVID-19 pandemic may have affected the newborn hearing screening program during the years covered by our study. According to information from authorized institutions, the infant hearing screening rates in Sivas decreased

from around 95% to 90%, similar to the nationwide trend during the COVID-19 pandemic in Turkey. Due to the increased workload on healthcare professionals during this period, it is essential to identify infants who were not screened for hearing loss. If hearing loss is detected later, prompt action can be taken immediately, even if the child has already started school.

The absence of immittance measurements for infants and the inability to access detailed information on risk factors for individuals with congenital hearing loss constitute the limitations of this study. In a retrospective study conducted by Bora et al. [22] between 2015 and 2017, evaluating 3490 newborns over 24 months, they reached TEOAE results for 2312 cases (66.2%), while 1178 cases (33.8%) did not have accessible test results. The study highlighted the incomplete nature of demographic data and emphasized the importance of the data recording system [22]. Given the still high rates of congenital hearing loss, screening data should be processed meticulously to ensure early diagnosis and treatment.

Limitations

The absence of extensive data on family history, prenatal factors, and environmental risks restricts the study. Its retrospective design impacts the thoroughness and reliability of its results. Additionally, being confined to a single province may not sufficiently represent national or international evaluations of neonatal hearing loss.

Conclusion

Implementing the hearing screening program in our country has been systematic and practical. A comprehensive analysis of newborn hearing screening data in our province over the last five years has indicated a congenital hearing loss rate of 0.48% for bilateral hearing loss and 0.68% overall. This rate aligns with findings reported in relevant literature. Early intervention is crucial for developing auditory functions and improving cognitive development. As a result, individuals with hearing loss can be integrated into society.

Disclosures

Acknowledgments: This study was presented as a poster at the 44th Turkish National Otorhinolaryngology and Head and Neck Surgery Congress, November 15-19, 2023, in Kaya Palazzo Congress Center, Belek-Antalya, Turkey.

Ethics Committee Approval: The study protocol (2023-06/26) was approved by the Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine.

Informed Consent: Not necessary for this manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept -; AA, Design -; AA, BŞ, MKŞ; Supervision -; AA; Materials -; AA, BŞ, MKŞ; Data Collection and Process in Supervision; AA, BŞ, MKŞ; Analysis and Interpretation -; AA; Literature Search -; AA, BŞ, MKŞ; Writing Manuscript -; AA, BŞ, MKŞ; Critical Review –AA, BŞ, MKŞ.

Conflict of Interest: The authors declare no potential conflict of interest relevant to this article.

Financial Disclosure: The authors declare that this study had no financial support.

References

1. Karaca ÇT, Toros SZ, Naiboğlu B, et al. Yenidoğan İşitme Taraması Sonuçlarımız. [Our Newborn Hearing Screening Results.] *Van Med J.* 2014;21(2):67-71.
2. Acar B, Ocak E, Acar M, Kocaöz D. Comparison of risk factors in newborn hearing screening in a developing country. *Turk J Pediatr.* 2015;57(4):334-8. PMID: 29984919.
3. Ohl C, Dornier L, Czajka C, et al. Newborn hearing screening on infants at risk. *Int J Pediatr Otorhinolaryngol.* 2009;73(12):1691-5. doi:10.1016/j.ijporl.2009.08.027.
4. Karaca CT, Oysu C, Toros SZ, et al. Is hearing loss in infants associated with risk factors? Evaluation of the frequency of risk factors. *Clin Exp Otorhinolaryngol.* 2014;7(4):260-3. doi:10.3342/ceo.2014.7.4.260.
5. Genç GA, Başar F, Kayıkçı ME, et al. Hacettepe Üniversitesi yenidoğan işitme taraması bulguları. [The findings of newborn hearing screening at Hacettepe University]. *J Pediatr Health Dis.* 2005;48(2):119-24.
6. Sarı K. Yenidoğan İşitme Tarama Testi Sonuçlarımız. [Our Newborn Hearing Screening Test Results]. *KBB-Forum.* 2021;20(2):115-21.
7. Turkmen AV, Yiğit O, Akkaya E, et al. İstanbul Eğitim ve Araştırma Hastanesi Yenidoğan İşitme Taraması Sonuçlarımız. [Newborn Hearing Screening Outcomes at Istanbul Education and Research Hospital]. *İstanbul Med J.* 2013;14:175-80.
8. Maris M, Venstermans C, Boudewyns AN. Auditory neuropathy/dyssynchrony as a cause of failed neonatal hearing screening. *Int J Pediatr Otorhinolaryngol.* 2011;75(7):973-5. doi:10.1016/j.ijporl.2011.04.012.
9. Yoshimura H, Okubo T, Shinagawa J, et al. Epidemiology, aetiology and diagnosis of congenital hearing loss via hearing screening of 153913 newborns. *Int J Epidemiol.* 2024;53(3):dyae052. doi:10.1093/ije/dyae052.
10. Hatzopoulos S, Cardinali L, Skarżyński PH, et al. The Otoacoustic Emissions in the Universal Neonatal Hearing Screening: An Update on the European Data (2004 to 2024). *Children (Basel).* 2024;11(11):1276. Published 2024 Oct 23. doi:10.3390/children11111276.
11. Zhou X, Wang L, Jin F, et al. The prevalence and risk factors for congenital hearing loss in neonates: A birth cohort study based on CHALLENGE study. *Int J Pediatr Otorhinolaryngol.* 2022;162:111308. doi:10.1016/j.ijporl.2022.111308.
12. Korver AM, Smith RJ, Van Camp G, et al. Congenital hearing loss. *Nat Rev Dis Primers.* 2017;3:16094. Published 2017 Jan 12. doi:10.1038/nrdp.2016.94.
13. Sabbagh S, Amiri M, Khorramizadeh M, et al. Neonatal hearing screening: Prevalence of unilateral and bilateral hearing loss and associated risk factors. *Cureus.* 2021;13(6):e15947. doi:10.7759/cureus.15947.
14. Thangavelu K, Martakis K, Fabian S, et al. Prevalence and risk factors for hearing loss in high-risk neonates in Germany. *Acta Paediatr.* 2019;108(11):1972-7. doi:10.1111/apa.14837.
15. Pourarian S, Khademi B, Pishva N, Jamali A. Prevalence of hearing loss in newborns admitted to the neonatal intensive care unit. *Iran J Otorhinolaryngol.* 2012;24(68):129-34.
16. Cristobal R, Oghalai JS. Hearing loss in children with very low birth weight: current review of epidemiology and pathophysiology. *Arch Dis Child Fetal Neonatal Ed.* 2008;93(6):F462-8. doi:10.1136/adc.2007.124214.
17. Li Y, Yang X, Wang C, et al. Analysis of audiological outcomes of children referred from a universal newborn hearing screening program over 9 years in Beijing, China. *Sci Rep.* 2023;13(1):22630. Published 2023 Dec 19. doi:10.1038/s41598-023-50171-8.
18. Kemaloğlu YK, Gökdoğan Ç, Gündüz B, et al. Newborn hearing screening outcomes during the program's first decade in a reference hospital from Turkey. *Eur Arch Otorhinolaryngol.* 2016;273(5):1143-9. doi:10.1007/s00405-015-3654-1.
19. Bolat H, Bebitoglu FG, Ozbas S, et al. National newborn hearing screening program in Turkey: struggles and implementations between 2004 and 2008. *Int J Pediatr Otorhinolaryngol.* 2009;73(12):1621-3. doi:10.1016/j.ijporl.2009.08.002.
20. Rockwell M, Gungor A, Pichilingue Reto P, et al. Neonatal hearing screening: Challenges of COVID-19 pandemic. *Clin Pediatr (Phila).* 2023;62(11):1380-4. doi:10.1177/00099228231158673.

21. Jenks CM, DeSell M, Walsh J. Delays in infant hearing detection and intervention during the COVID-19 pandemic: Commentary. *Otolaryngol Head Neck Surg.* 2022;166(4):603-4. doi:10.1177/01945998211067728.

22. Bora A, Durmuş K, Altuntaş EE. Retrospective evaluation of newborn hearing screening results and importance of patient record system. *Cumhuriyet Med J.* 2018;40(3):276-83. doi:10.7197/223.vi.414052.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Analysis of cancellations of surgery for benign prostatic hyperplasia after patients are taken to the operating room: A retrospective single-center study

Vildan Kolukcu[a,*], Fatih Firat[b]

[a] *Tokat Gaziosmanpaşa University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Tokat, Türkiye*
[b] *Tokat Gaziosmanpaşa University, Faculty of Medicine, Department of Urology, Tokat, Türkiye*

ARTICLE INFO

Keywords:
Benign prostatic hyperplasia
Elective surgery
Cancellation
Perioperative care
Pre-operative management
Operating room

Received: Sep 29, 2024
Accepted: Mar 17, 2025
Available Online: 25.04.2025

DOI:
10.5455/annalsmedres.2024.09.208

Abstract

Aim: This study aims to evaluate the reasons for canceling elective surgeries for benign prostatic hyperplasia (BPH) after patients are taken to the operating room.

Materials and Methods: Data from 1743 cases scheduled for elective surgery due to BPH that were taken to the operating room between December 2011 and June 2024 were retrospectively analyzed. The demographic data, American Society of Anesthesiologists (ASA) status, reasons for cancellation. The clinical course of the 89 patients (5.1%) whose surgeries were canceled in the operating room were evaluated.

Results: The mean age of the patients whose surgeries were canceled in the operating room was 69.2 ± 11.68 years. The most common reasons for surgical cancellations were cardiovascular system-related pathologies, such as uncontrolled hypertension (33.7%) and abnormal electrocardiographic changes (12.4%). Eighty-five (95.5%) patients had an ASA status of 3 or higher. The surgeries of 80 (89.9%) patients were successfully performed at a later date in our hospital. It was determined that 87.64% of the cancellations could have been avoidable.

Conclusion: Our study found that 5.1% of elective surgeries due to BPH were cancelled, and most were avoidable. We believe that rigorous and optimized preoperative patient assessment is crucial in preventing surgical cancellations, especially in procedures involving an elderly population, such as surgeries for BPH.

Introduction

Benign prostatic hyperplasia (BPH) is the proliferative process of the stromal and epithelial components of the gland. Prostate enlargement and bladder outlet obstruction are the main clinical symptoms of BPH. , The prevalence of BPH-related lower urinary tract symptoms continues to increase as the worldwide population ages [1,2]. BPH, which is one of the most common health problems among aging men, can be managed through several approaches, including watchful waiting, lifestyle modifications, pharmacological treatments, and surgical intervention [3,4]. If left untreated, BPH can lead to complications such as refractory urinary retention, obstructive uropathy, bladder stones, and recurrent urinary tract infections [5,6]. Large-scale studies report that the annual rate of surgery for BPH is around 7.5% [4]. Despite the development of new surgical techniques for BPH and developments in preoperative patient care, perioperative cancellations are an essential problem in current practice.

In many developed countries, surgical waiting times are considered a critical indicator of the quality of the healthcare system. Particularly, the cancellation of operations once patients are inside the operating room leads to inefficient use of hospital resources, delays in surgical planning, and emotional distress for patients [7,8]. Therefore, developing effective strategies to minimize surgery cancellations is very important [9]. Recent clinical studies have focused on reducing cancellations by optimizing hospital capacity and minimizing the psychological impact of surgical stress on patients [7,9]. These studies highlight that a significant portion of cancellations of elective surgeries can be prevented through meticulous preoperative coordination [9].

However, there is limited literature on the specific factors leading to elective surgery cancellations after patients have been taken to the operating room. This study aims to analyze the causes of patient cancellations of surgeries for BPH. We aimed to analyze this critical health issue among

*Corresponding author:
Email address: vildankolukcu@gmail.com (Vildan Kolukcu)

the elderly population. While we have conducted a thorough search of the English literature, this study is, to the best of our understanding, the first to report on cancellations of BPH surgeries after patients have entered the operating room.

Materials and Methods

Data from 1743 patients who were scheduled for elective surgery due to BPH and admitted to the operating room at our institution between December 2011 and June 2024 were analyzed retrospectively. Elective surgeries for BPH included open prostatectomy, transurethral resection of the prostate, and transurethral incision of the prostate. All patients underwent routine preoperative evaluations at the anesthesia outpatient clinic at the time of their scheduled operation, which included laboratory blood tests, physical examination findings, electrocardiograms, and chest X-rays. In total, procedures of 89 patients (5.1%) were canceled after the patient entered the operating room. The demographic data, American Society of Anesthesiologists (ASA) status, reasons for cancellation, and clinical courses of whose surgeries were canceled in the operating room were analyzed.

Cancellations were categorized into two groups: patient-related reasons and hospital-related reasons. Additionally, the reasons for cancellation were classified as avoidable or unavoidable. The classification of arterial hypertension was made according to current guidelines. Patients with systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg were considered to have stage 3 or more severe hypertension, and their surgeries were canceled as suggested by the guidelines [9]. Furthermore, the surgeries of patients with abnormal electrocardiograms detected during preoperative monitoring were canceled, and these patients were subsequently referred to the cardiology department. Similarly, patients with abnormal hormonal and biochemical results documented in the operating room were referred to the endocrinology department. On the other hand, patients with oral herpes, positive urine culture, and upper or lower respiratory tract infections detected preoperatively were referred to the infectious diseases department. We also analyzed the subsequent surgeries to determine whether the patients who received subsequent surgery at the same center.

The study was approved by Tokat Gaziosmanpasa University Local Ethics Committee (24- KAEK-225).

Statistical analysis

We performed descriptive analysis in the present study. The continuous variabşes are expressed in mean and standard deviation. The categorical variables are expressed in number of affected individuals and the percentage of the study population. The normal distrinution of the continuous variables were evaluated using Kolmogorov-Smirnov test. Any p value less than 0.05 were defined as statistical significance. All statistical analyses were performed on the Statisrical software Package for Social Sciences version 22 (SPSSv22, IBM, USA)

Results

The data of 1743 patients admitted to the operating room for elective surgery due to BPH were retrospectively analyzed. In total, 179 open prostatectomies, 1468 transurethral resection of the prostate, and 96 transurethral incision of the prostate were planned. The surgeries of 89 patients (5.1%) were canceled in the operating room. Of these, 2 patients (2.3%) were scheduled for transurethral incision of the prostate, 26 (29.2%) for open prostatectomy, and 61 (68.5%) for transurethral resection of the prostate. The mean age of the patients whose surgeries were canceled was 69.2 ± 11.68 years. Four patients (4.5%) were classified as ASA 2, 63 (70.8%) as ASA 3, and 22 (24.7%) as ASA 4. No patient was classified as ASA 1.

Surgery cancellations in 74 patients (83.1%) were due to patient-related factors. A total of 30 patients (33.7%) had their surgeries canceled due to uncontrolled hypertension. All these patients had a history of antihypertensive medication use, and only 4 (13.3%) were found to be noncompliant with their treatment. Intraoperative abnormal electrocardiographic changes led to the cancellation of surgeries in 11 patients (12.4%). Of these, 1 patient (9.1%) had a newly diagnosed bundle branch block, 3 patients (27.3%) atrial fibrillation, 4 (36.3%) had frequent ventricular extrasystoles, and 3 (27.3%) showed ST-segment changes. Infectious causes were responsible for the cancellation of surgeries in 20 patients (22.4%). Among these, 9 patients had upper respiratory tract infections, 4 had lower respiratory tract infections, 5 had oral herpetic infections, and 2 had urinary tract infections. One patient (1.1%) had blood glucose levels above 400 mg/dL, which led to the cancellation of the surgery. Additionally, 7 patients (7.9%) had their surgeries canceled due to smoking on the day of surgery, and 5 patients (5.6%) due to issues with adherence to anticoagulant therapy protocols (Table 1).

Fifteen (16.9%) procedures were cancelled due to hospital-related reasons. In one patient (1.1%), surgery was canceled due to failure of surgical equipment during final preoperative testing. Surgeries of 7 patients (7.9%) were canceled due to over-booking, and the operating theatre time was exceed . Surgical procedures for three patients (3.4%) were canceled intraoperatively due to the unavailability of intensive care unit beds. Similarly, four procedures (4.5%) were canceled due to inadequate blood preparation, attributed to coordination deficits with the blood bank. While 87.64% of the cancellations were considered avoidable, 80 patients (89.9%) were successfully rescheduled for surgery at our hospital.

Discussion

The incidence of BPH in individuals over 50 years of age is approximately 30% and the incidence increases with the age of the individuals. BPH frequently causes lower urinary tract symptoms [3]. It affects more than 70% of men over the age of 70. The socioeconomic burden of BPH is substantial, casuing a burden of over 3 billion dollars annually on the healthcare system .As the life expectancy of the individuals is rising the incidence of BPH is increasing [10]. In our country by the year 2040, the total elderly population is estimated to increase from 8% today to 16.3% . This indicates that healthcare professionals will

Table 1. Reasons for cancellation of surgery.

Variables	Reasons for Cancelation of surgery	Percentage of canceled cases
Patient-related causes	Stage 3 or 4 hypertension	30 (33.7%)
	Electrocardiographic changes	11 (12.4%)
	Upper respiratory tract infections	9 (10.1%)
	Oral herpetic infections	5 (5.6%)
	Lower respiratory tract infections	4 (4.5%)
	Urinary tract infections	2 (2.2%)
	Smoking	7 (7.9%)
	On anticoagulant medications	5 (5.6%)
	High blood sugar levels	1 (1.1%)
Hospital-related causes	Over-booking	7 (7.9%)
	Lack of blood	4 (4.5%)
	Lack of intensive care unit beds	3 (3.4%)
	Lack of equipment	1 (1.1%)

face BPH more frequently [4]. For this reason, preoperative anesthesia preparation and prevention of cancellation of the procedure in the operating room are of increasing importance in patients with BPH.

Cancellation of elective procedures have a very negative impact on operating room efficiency and impose a significant economic burden on the healthcare system. Additionally, this situation decreases patient satisfaction and lowers staff morale [11]. Perroca et al. [12] stated that the average cost of surgery cancellations per patient was reported to be $ 29.54 In another study, Dexter et al. [13] reported that each minute of delay in the operating room at Stanford University Medical Center cost the finance department approximately $8.13. Moreover, surgery cancellations cause a backlog of patient appointments. Additionally, the psychological impact on both the patients and the surgical team is another negative aspect of cancellation of surgeries.

Leslie et al. [8] showed that in15,444 elective surgeries, reported that the urology department had the highest cancellation rate at 9.53% . In another study, Chiu et al. [14] evaluated the cancellations of elective surgeries and reported that the urology clinic ranked second among all surgeries with a cancellation rate of 13%. Argo et al showed that the urology department had a 14% cancellation rate, ranking in the top three [11]. Similarly, Özcan et al reported that urological surgery cancellations were the third most common among all surgery cancellations [9]. A multidisciplinary approach and preoperative evaluation have reduced elective surgery cancellations [9,12]. Previous studies have reported that approximately 60% of elective surgery cancellations are due to potentially avoidable factors [12]. In a clinical study analyzing surgery cancellations in an orthopedic clinic, it was observed a 42.9% reduction in cancellation rates following improvements in healthcare services [15]. Hori et al. [7] reported that the rate of surgery cancellations in the operating room was below 0.01%, that was attributed to patients undergoing medical examination and evaluation by an anesthesiologist the day before surgery. Surgery cancellations in the operating room are particularly critical due to the emotional stress it causes for patients and the unnecessary loss of time and resources for the healthcare system [9].

Surgery cancellation causes vary depending on the demographic characteristics of the patient population and the surgical procedure [7,9]. In the pediatric age group, the most common cause is upper respiratory tract infections, while in the elderly population, metabolic and cardiac reasons are more prevalent [9,16]. Perroca et al. [12] more than half of the surgery cancellations were attributed to patient-related factors . Similarly, Chang et al. [16] reported that the most important cause of surgery cancellations was patient-related medical problems, accounting in 59% of the cases. In our study, %83.1 of cancellations were due to the medical conditions of the patients. Specifically, cardiac problems, which were associated with the advanced age of the patients scheduled for surgery, were frequent causes of cancellation. Similarly, Özcan et al. showed that more than half of the surgery cancellations were directly related to the cardiovascular system [9].

One common cause of surgery cancellations is insufficient operational capacity. Yoon et al. [17] evaluayed 2,494 patients and showed that more than 20% of the surgeries were canceled, with nearly one-third of the cancellations attributed to insufficient operational capacity. Similarly, in the study by Pollard et al. [18], the surgery cancellation rate was reported to be 13%, and nearly one-fifth of the cancellations were due to insufficient operating room hours . In our study, over-booking was observed in only 7 patients (7.9%), which we attribute to the fact that our university hospital has more spacious operating room conditions. In the study by Shah et al. [19], it was reported that 10.3% of surgery cancellations were due to surgeon unavailability. In the study by Lopez et al [20], it was documented that 5% of surgery cancellations were related to the surgical team . In our study, this rate was 1.1%. We believe that this is related to the fact that we work with a large urology team in a faculty hospital. In another study, 2.42% of surgery cancellations were attributed to the insufficiency of the intensive care unit [12]. In a similar study, Livingstone et al. [21] reported that 2.5% of surgery cancellations were due to bed shortages . In our study, surgery cancellations due to unexpected intensive care unit needs related to the patient's clinical condition

occurred in only 3 patients (3.4%) on the operating table. Apart from that, there were no surgery cancellations due to bed shortages in the urology department.

Infectious pathologies are a significant cause of surgical cancellations. Studies report varying rates: 7% in a national study of adults [9], 12.8% due to upper respiratory tract infections (URTIs) [22], and 18% overall, primarily from respiratory infections [23]. In our study, 22.4% of cancellations were attributed to infections, with respiratory infections being the most common.

Limitations

The small patient volume and the retrospective nature of the analysis are the main limitations of our research. Our study needs to be developed prospectively involving higher patient numbers.

Conclusion

Intraoperative surgical cancellations significantly impact the healthcare system. The resulting emotional distress for patients, families, and surgical teams, coupled with prolonged surgical schedules and inefficient resource utilization, are critical consequences. In our study, 5.1% of elective benign prostatic hyperplasia (BPH) surgeries were canceled intraoperatively. Notably, a significant proportion of these cancellations were due to preventable causes.

Disclosures

Ethics Committee Approval: Ethical approval was obtained for this study from the Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee (24-KAEK-225).

Informed Consent: Not necessary for this manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: VK, FF, Design: VK, FF; Supervision: VK, FF; Materials: VK, FF; Data Collection and/or Processing: VK, FF; Analysis and Interpretation: VK, FF; Literature Review: VK, FF; Writing Manuscript: VK, FF; Critical Review: VK, FF.

Conflict of Interest: There are no potential conflicts of interest in this study.

Financial Disclosure: No financial support was received from any institution or person related to the study.

References

1. Atan A. Combination treatments in benign prostatic hyperplasia. *Androl Bul.* 2021;23:30-36. https://doi.org/10.24898/ tandro.2021.05945.
2. Bulut EC, Atan A. Pathophysiology of BPH. *Androl Bul.* 2023;25(3):181-9. https://dx.doi.org/10.24898/tandro.2023.91328.
3. Nunes RLV, Antunes AA, Constantin DS. Contemporary surgical treatment of benign prostatic hyperplasia. *Rev Assoc Med Bras.* (1992) 2017;63(8):711-6. https://doi.org/10.1590/1806-9282.63.08.711.
4. İbis MA, Cayan S, Tokatli Z, et al. Trends in benign prostatic hyperplasia surgery over the years: A multicenter 14-year retrospective study. *Turk J Urol.* 2021;47(6):501-8. https://doi.org/10.5152/tud.2021.21262.
5. Kim EH, Larson JA, Andriole GL. Management of Benign Prostatic Hyperplasia. *Annu Rev Med.* 2016;67:137-51. https://doi.org/10.1146/annurev-med-063014-123902.
6. Yalcin K. Comparison of three techniques in bladder stone surgery: Which technique is more effective and safe? *Niger J Clin Pract.* 2023;26(8):1128-33. https://doi.org/10.4103/njcp.njcp_9_23.
7. Hori Y, Nakayama A, Sakamoto A. Surgery cancellations after entering the operating room. *JA Clin Rep.* 2016;2(1):40. https://doi.org/10.1186/s40981-016-0066-1.
8. Leslie RJ, Beiko D, Vlymen JV, Siemens DR. Day of surgery cancellation rates in urology: Identification of modifiable factors. *Can Urol Assoc J.* 2013;7(5-6):167-73. https://doi.org/10.5489/cuaj.12020.
9. Özcan MS, Özden ES, Solmaz FA, Kösem A, Akyol Y, Kırdemir P. Prevalence and Causes of Elective Surgery Cancellations After Patients are Taken to the Operating Room: A Prospective, Cross-Sectional Study. *Turk J Anaesthesiol Reanim.* 2024;52(1):14-21. https://doi.org/10.4274/tjar.2024.231454.
10. Lee YJ, Lee JW, Park J, et al. Nationwide incidence and treatment pattern of benign prostatic hyperplasia in Korea. *Investig Clin Urol.* 2016;57(6):424-30. https://doi.org/10.4111/icu.2016.57.6.424.
11. Argo JL, Vick CC, Graham LA, Itani KMF, Bishop MJ, Hawn MT. Elective surgical case cancellation in the Veterans Health Administration system: identifying areas for İmprovement. *Am J Surg.* 2009;198(5):600-6. https://doi.org/10.1016/j.amjsurg.2009.07.005.
12. Perroca MG, Jericó MC, Facundin SD. Surgery cancelling at a teaching hospital: implications for cost management. *Rev Lat Am Enfermagem.* 2007;15(5):1018-24. https://doi.org/10.1590/s0104-11692007000500021.
13. Dexter F, Macario A. Applications of information systems to operating room scheduling. *Anesthesiology.* 1996;85(6):1232–4. https://doi.org/10.1097/00000542-199612000-00002.
14. Chiu CH, Lee A, Chui PT. Cancellation of elective operations on the day of intended surgery in a Hong Kong hospital: point prevalence and reasons. *Hong Kong Med J.* 2012;18(1):5-10. PMID: 22302904.
15. Abdellaoui A, Addison A. A study of cancelled operations in an orthopaedics department. Clin Gov Bull 2005; 5(6): 6-9.
16. Chang JH, Chen KW, Chen KB, Poon KS, Liu SK. Case review analysis of operating room decisions to cancel surgery. *BMC Surg.* 2014;14:47. https://doi.org/10.1186/1471-2482-14-47.
17. Yoon SZ, Lee SI, Lee HW, Lim HJ, Yoon SM, Chang SH. The effect of increasing operating room capacity on day-of-surgery cancellation. *Anaesth Intensive Care.* 2009;37(2):261-6. https://doi.org/10.1177/0310057x0903700203.
18. Pollard JB, Olson L. Early outpatient preoperative anesthesia assessment: does it help to reduce operating room cancellations? *Anesth Analg.* 1999;89(2):502-5. https://doi.org/10.1097/00000539-199908000-00048.
19. Shah J, Ansari A, Bhattacharyya J. Cancellation of urology Operations. Clinical Governance: *An International Journal.* 2006;11(2):128-133. https://doi.org/10.1108/14777270610660501.
20. Lopez RN, Jowitt S, Mark S. The reasons for cancellation of urological surgery: a retrospective analysis. *N Z Med J.* 2012;125(1359):17-22. PMID: 22932510.
21. Livingstone JI, Harvey M, Kitchin N, Shah N, Wastell C. Role of pre-admission clinics in a general surgical unit: a 6-month audit. *Ann R Coll Surg Engl.* 1993;75(3):211-2. PMID: 8323221. PMCID: PMC2497874.
22. Mesmar M, Shatnawi NJ, Faori I, Khader YS. Reasons for cancellation of elective operations at a major teaching referral hospital in Jordan. *East Mediterr Health.* J 2011;17(8):651-5. PMID: 21977567.
23. González-Arévalo A, Gómez-Arnau JI, delaCruz FJ, et al. Causes for cancellation of elective surgical procedures in a Spanish general hospital. *Anaesthesia.* 2009;64(5):487-93. https://doi.org/10.1111/j.1365-2044.2008.05852.x.
24. Spazzapan M, Javier P, Abu-Ghanem Y, et al. Reducing last-minute cancellations of elective urological surgery-effectiveness of specialist nurse preoperative assessment. *Int J Qual Health Care.* 2023;35(1):1-6. https://doi.org/10.1093/intqhc/mzad008.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Prognostic value of the lymphocyte-albumin index combined with PSI score in predicting mortality in severe community-acquired pneumonia

Gulsum Altuntas

Fırat University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Elazığ, Türkiye

ARTICLE INFO

Keywords:
Pneumonia severity index
Lymphocyte albumin index
Severe community-acquired pneumonia
Prediction
Intensive care units

Received: Feb 10, 2025
Accepted: Mar 19, 2025
Available Online: 25.04.2025

DOI:
10.5455/annalsmedres.2025.02.038

Abstract

Aim: Severe community-acquired pneumonia (SCAP) is a leading cause of sepsis, septic shock, and mortality. Various prognostic scoring systems are used for evaluation, but their use and availability may be complex. Our objective was to evaluate the prognostic significance of LAI, which is easy and inexpensive to perform, and the importance of its combination with PSI score in predicting the mortality of patients with SCAP.

Materials and Methods: This is a retrospective, single-center, cross-sectional study. The patients aged ≥18 with SCAP in tertiary intensive care units were analyzed. Data from patient files and the hospital database include demographic data, PSI score, SOFA, GCS, APACHE II, laboratory parameters, and clinical variables. Cut-off values were used to assess the predictive accuracy of each predictor, measured by the area under the ROC curve (AUC) with a 95% confidence interval (CI). Additionally, we developed combined models for PSI+LAI utilizing various logistic regression analyses. Factors associated with mortality were analyzed using multivariate logistic regression analysis.

Results: The cut-off value of 110 for PSI was a good predictor with 97.8% sensitivity and 98.7% specificity. The cut-off value of 3379 for LAI was observed to be a good predictor of mortality with 92.5% sensitivity and 90.7% specificity. The AUC value for PSI was 0.987 and the AUC value for LAI was 0.933. The AUC value obtained when PSI and LAI values were evaluated together was 0.997. In multivariate analysis, high PSI score, low pulse rate, and LAI value constitute a risk for mortality.

Conclusion: Although PSI or LAI have a high predictive accuracy, their combined use may improve this accuracy and allow for more reliable management of SCAP patients. The PSI score offers a comprehensive assessment. This, combined with the faster and easier application of LAI, provides great advantages to clinicians.

Introduction

Severe Community-Acquired Pneumonia (SCAP) can be lethal by progressing to sepsis, septic shock, and then mortality [1]. Mortality remains high despite rapid diagnostic tests, advanced vaccination strategies, and all modern approaches and treatments [2]. Mortality rates reach 30% in the intensive care units (ICU) [3]. *Streptococcus pneumoniae*, *gram-negative bacteria*, and *Methicillin-Resistant Staphylococcus Aureus* are the pathogens causing SCAP [4,5].

Patients who do not respond to standard oxygen and fluid therapy and require mechanical ventilation (MV) or vasopressor support are considered to have SCAP [6]. Severe CAP is diagnosed with clinical findings, radiological imaging, and laboratory tests. Pneumonia severity index (PSI), CURB-65, and A-DROP Score are used to predict prognosis [7]. However, their use and availability are complex. The utility of various biochemical tests to predict the prognosis and optimize the treatment plan in this patient group is gradually gaining importance. These tests are crucial for identifying high-risk patients, ensuring appropriate and timely treatment, and ultimately reducing morbidity and mortality.

Until now, many biomolecules have been studied to predict the prognosis of SCAP. For example, procalcitonin is associated with morbidity and mortality in bacterial pneumonia [8]. In combination with the clinical parameters, procalcitonin is also used to guide altering the antibiotic treatment for SCAP. However, biomarkers including C-reactive protein (CRP), copeptin, adrenomedullin, and D-Dimer have been used, but their advantage over one an-

*Corresponding author:
Email address: galtuntas06@hotmail.com (Gulsum Altuntas)

other has not been confirmed [9]. A complete blood count is a cheap and simple test that is easy to perform. To date, ratios of various parameters in complete blood count have been studied in the course of pneumonia as in many other diseases [10,11]. An elevated neutrophil count and lymphopenia are frequently observed in bacterial pneumonia [12]. In addition, lymphopenia was shown to increase the mortality rate in SCAP [13]. However, serum albumin is a negative acute-phase reactant that decreases with increasing severity of inflammation. It also provides insight into the patient's nutritional status. Studies have shown that low albumin value is related to increased mortality in patients with SCAP as well as in various inflammatory diseases [14].

A negative correlation between the severity of inflammation and both lymphocyte count and albumin concentration has been observed [15]. The Lymphocyte Albumin Index (LAI), calculated by multiplying lymphocyte count by albumin concentration, was initially identified as a reliable prognostic marker in stage II/III rectal cancer [16].

This research focuses on evaluating the prognostic role of LAI, which is an easily applicable and low-cost parameter, and the importance of its combination with PSI score predicting mortality of patients with SCAP.

Materials and Methods

Study design and patients

This research is a single-center, retrospective cross-sectional study. The patients aged ≥18 years with SCAP hospitalized in tertiary intensive care units between January 2018 and October 2024 were retrospectively analyzed. Ethical approval was granted with the date and number 27.12.2024-29971. Our study was conducted according to the Helsinki Declarations and Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines. Informed consent was not obtained due to the study's retrospective design.

Exclusion criteria

Exclusion criteria included age under 18 years, ICU stay less than 48 hours with COVID-19 pneumonia, hematological disorders, extrapulmonary infections, infections occurring ≥48 hours post-hospitalization or intubation (including referred patients), and incomplete data.

Data collection

Demographic data, PSI score, Glasgow Coma Score (GCS), Sequential Organ Failure Assessment Score (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, laboratory parameters (CRP, Procalcitonin, Albumin, Platelet, Neutrophil, Lymphocyte, pH, pCO_2, pO_2, Lactate) in the first 24 hours of intensive care admission, were recorded from the hospital database. Clinical variables (pulse rate, respiratory rate, systolic and diastolic blood pressure, intubation/mechanical ventilation, vasopressor requirement, and mortality) were retrieved from the electronic database of the hospital. Comorbidities were recorded from patient files according to the Charlson Comorbidity Index.

LA index was calculated as lymphocyte count (10^3/μL) x serum albumin (g/dL) level.

Diagnosis of severe community-acquired pneumonia

The 2007 guidelines from the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) state that diagnosing severe community-acquired pneumonia and determining the need for ICU admission of the patient requires either one major criterion or at least three minor criteria.

Minor criteria

- Respiratory rate ≥30/min. - PaO_2/FIO_2 ≤250 - Multilobar infiltration - Confusion/disorientation - Uremia (BUN ≥20 mg/dL) - Leukopenia (Leukocyte <4.000/μl) - Hypothermia (<36 C^o) - Hypotension requiring intensive fluid administration.

Major criteria

- Respiratory failure necessitating invasive mechanical ventilation - Sepsis that requires vasopressor support.

The diagnosis of SCAP was made by an experienced intensive care specialist working in our intensive care unit.

PSI score

The Pneumonia Severity Index (PSI) score is a comprehensive assessment tool that incorporates demographic data, comorbidities, clinical findings, laboratory results, and radiological imaging. In our study, the PSI score was calculated and documented in line with the literature by an experienced specialist in the intensive care unit on the first day of admission. This data was sourced from the hospital database. Patients without physical examination findings, accompanying diseases, or laboratory results are classified as class I; those scoring ≤70 points are class II; 71-90 points are class III; 91-130 points are class IV; and scores >130 points are class V [17]. In this study, classes I-III were deemed low risk, while classes IV-V were regarded as high risk.

Endpoints

Primary endpoint: the significance of the LAI in predicting 30-day mortality. Secondary endpoints: a comparison of the importance of LAI, PSI, and LAI+PSI measurements in predicting mortality.

Statistical analysis

The sample size was calculated using the G*Power 3.1.9.2 software for logistic regression analysis. In this calculation, the odds ratio (OR) value was determined as 2.87, the significance level (α) as 0.05, and power (1 - β) as 0.95. As a result of the analysis, the minimum number of subjects that needed to be included in the study was determined as 86.

Statistical analyses were performed using Statistical software Package for Social Sciences version 22 (SPSSv22, Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables. Categorical variables are expressed as frequencies (n) and percentages (%), whereas continuous data are reported as mean ± standard deviation (Mean ±

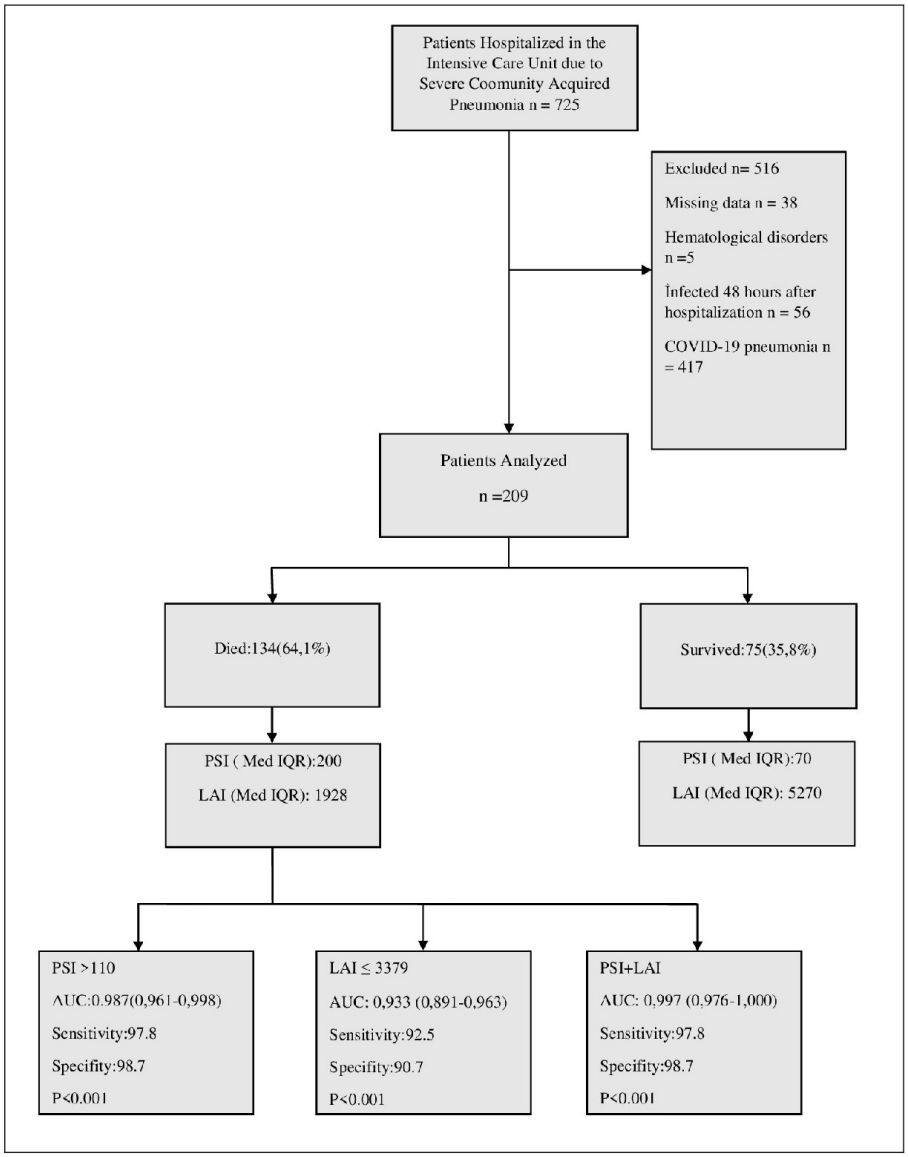

Figure 1. Flow-chart for the process of patient selection.

SD) or median with interquartile range (IQR) (25^{th}-75^{th} percentiles). Differences in categorical variables between groups were evaluated using Pearson's Chi-square test. T and the Mann-Whitney U-test were utilized for comparisons of variables between two independent groups.

Receiver operating characteristic (ROC) curve analysis was conducted to assess mortality, with specific cut-off values determined for each predictive continuous parameter. The area under the ROC curve (AUC) and the corresponding 95% confidence interval (CI) were used to determine the predictive performance of each variable. Additionally, logistic regression models integrating PSI and LAI were developed to enhance prediction accuracy.

Mortality risk factors were identified using multivariate logistic regression. This process began with univariate logistic regression to screen for potential associations between risk factors and mortality. Variables exhibiting a p-value <0.05 in the univariate analysis were included in a preliminary multivariate model, which was refined through backward stepwise selection. Spearman's correlation analysis was also employed to examine inter-variable relationships, with statistical significance defined as $p<0.05$.

Results

In this study, a total of 725 patients were admitted to our tertiary intensive care units between January 2018 and October 2024 due to SCAP. Of the patients, 38 were excluded due to lack of data, five due to hematological disease, 417 due to COVID-19 pneumonia diagnosis, and 56 due to the development of pneumonia 48 hours after hospitalization (patients referred from other centers) (Figure 1). A total of 209 patients were included. Eighty-five (40.7%) were female, with an average age of 69.0 ± 16.8 years.

Comparison of mortality of patients

Hundred and thirty-four (64.1%) patients died due to SCAP. Charlson ($p<0.001$), APACHE II ($p<0.001$), SOFA ($p<0.001$), and PSI ($p<0.001$) scores of the deceased patients were significantly higher, and the GCS score

Table 1. Comparison of all parameters in patients with and without mortality.

		Deceased		Survived	
		n	%	n	%
Gender	Female	54	40.3	31	41.3
	Male	80	59.7	44	58.7
PSI Group	Low Group	2	1.5	69	92.0
	High Group	132	98.5	6	8.0
Vasopressor	Needed	75	56.0	10	13.3
	Not needed	59	44.0	65	86.7
Mechanical Ventilation	Needed	96	71.6	24	32.0
	Not needed	38	28.4	51	68.0
Age (years) Median (IQR)		72.0 (62.0-81.0)		71.0 (53.0-83.0)	
Charlson Index Median (IQR)		5.5 (3.0-8.0)		4.0 (3.0-6.0)	
GCS Median (IQR)		8.0 (5.0-12.0)		11.0 (8.0-14.0)	
APACHE II Median (IQR)		27.0 (21.0-32.0)		18.0 (14.0-24.0)	
SOFA Median (IQR)		11.0 (8.0-13.0)		7.0 (4.0-9.0)	
PSI Score Median (IQR)		200.0 (170.0-220.0)		70.0 (60.0-80.0)	
Pulse rate (Beats/minute) Median (IQR)		123.5 (103.0-140.0)		107.0 (95.0-120.0)	
Systolic Pressure (mmHg) Median (IQR)		89.5 (72.0-114.0)		120.0 (103.0-141.0)	
Diastolic Pressure (mmHg) Median (IQR)		52.0 (42.0-64.0)		68.0 (58.0-81.0)	
Respiratory Rate (Breaths/minute) Median (IQR)		36.0 (31-41)		32.0 (29-39)	0.002**
Platelet (10^3/μL) Median (IQR)		204 (115-294)		242 (194-317)	0.047**
Neutrophil (10^3/μL) Median (IQR)		10.93 (6.52-16.68)		11.07 (6.73-16.77)	0.944**
Lymphocyte (10^3/μL) Median (IQR)		0.74 (0.48-0.88)		1.5 (1.25-1.76)	<0.001**
Albumin (g/dL) Median (IQR)		2.8 (2.5-3.1)		3.5 (3.1-3.9)	<0.001**
C-Reactive Protein (mg/L) Median (IQR)		131 (65-186)		106 (38-166)	0.044**
Procalcitonin (mg/mL) Median (IQR)		2.1 (.6-7.6)		1. (.4-4.2)	0.040**
pH Median (IQR)		7.28 (7.2-7.38)		7.34 (7.29-7.42)	<0.001**
PCO_2 (mmHg) Median (IQR)		48.6 (33.5-64)		44.5 (32.6-55)	0.059**
PaO_2 (mmHg) Median (IQR)		52.2 (42-67)		56.2 (48-68.4)	0.087**
Lactate (mmoL/L) Median (IQR)		3.6 (2.2-5.6)		2.6 (1.6-4.2)	<0.001**
LAI Median (IQR)		1928 (1323-2484)		5270 (4257-6435)	<0.001**

*Square analysis, **Mann Whitney U test was applied. PSI: pneumonia severity index; GCS: Glasgow Coma Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment Score; LAI: Lymphocyte-Albumin Index.

Table 2. Area under the curve, sensitivity, and specificity of the optimal cut-off value of various predictors for mortality.

	AUC (95% CI)	p	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)
APACHE	0.766 (0.702-0.821)	**<0.001**	>24	64.9 (56.2-73.0)	78.7 (67.7-87.3)
SOFA	0.789 (0.727-0.842)	**<0.001**	>9	61.9 (53.2-70.2)	81.3 (70.7-89.4)
PSI	0.987 (0.961-0.998)	**<0.001**	>110	97.8 (93.6-99.5)	98.7 (92.8-100.0)
LA	0.933 (0.891-0.963)	**<0.001**	≤3379	92.5 (86.7-96.4)	90.7 (81.7-96.2)
PSI+LA	0.997 (0.976-1.000)	**<0.001**	-	97.8 (93.6-99.5)	98.7 (92.8-100.0)

AUC: Area Under Curve; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment Score; LAI: Lymphocyte-Albumin Index; PSI: Pneumonia Severity Index.

Table 3. Logistic regression analysis regarding the risk factors of mortality.

	B	p	OR	%95 CI
PSI Score	0.125	**0.001**	1.133	1.052-1.219
Pulse Rate (Beats/minute)	-0.060	**0.047**	0.942	0.887-0.999
LAI	-0.001	**0.006**	0.999	0.998-0.999

LAI: Lymphocyte-Albumin Index; PSI: pneumonia severity index.

(p<0.001) was significantly lower. The rate of high PSI scores in the patients with mortality (98.5%) was significantly higher than the rate in the patients who were alive (p<0.001). The need for vasopressors (p<0.001)

Table 4. Correlation analyses of the scores.

		PSI Score	LAI	Charlson	APACHE II	SOFA
LAI	r	**-0.696**				
	p	**<0.001**				
Charlson	r	**0.256**	**-0.158**			
	p	**<0.001**	**0.022**			
APACHE II	r	**0.555**	**-0.379**	**0.292**		
	p	**<0.001**	**<0.001**	**<0.001**		
SOFA	r	**0.556**	**-0.362**	**0.292**	**0.842**	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	
Age (Years)	r	**0.181**	**-0.160**	0.061	**0.148**	0.070
	p	**0.009**	**0.021**	0.384	**0.032**	0.314
Pulse Rate (Beats/minute)	r	**0.309**	**-0.171**	0.090	**0.398**	**0.350**
	p	**<0.001**	**-0.014**	0.194	**<0.001**	**<0.001**
Systolic Pressure (mmHg)	r	**-0.426**	**0.300**	-0.129	**-0.545**	**-0.463**
	p	**<0.001**	**<0.001**	0.063	**<0.001**	**<0.001**
Diastoilic Pressure (mmHg)	r	**-0.442**	**0.297**	**-0.151**	**-0.522**	**-0.478**
	p	**<0.001**	**<0.001**	**0.029**	**<0.001**	**<0.001**
Respiratory Rate (Breaths/minute)	r	**0.253**	-0.083	0.006	**0.301**	**0.243**
	p	**<0.001**	0.231	0.932	**<0.001**	**<0.001**
Albumin (g/dL)	r	**-0.624**	**0.662**	**-0.168**	**-0.398**	**-0.395**
	p	**<0.001**	**<0.001**	**0.015**	**<0.001**	**<0.001**
C-Reactive Protein (mg/L)	r	**0.138**	**-0.192**	0.012	-0.002	-0.008
	p	**0.047**	**0.005**	0.863	0.973	0.903
Procalcitonin (mg/mL)	r	**0.200**	**-0.197**	0.093	**0.156**	**0.145**
	p	**0.004**	**0.004**	0.180	**0.024**	**0.037**

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment Score; LAI: Lymphocyte-Albumin Index; PSI: Pneumonia Severity Index.

and MV ($p<0.001$) were significantly higher in the deceased than in the non-deceased. Pulse rate ($p<0.001$), respiratory rate ($p=0.002$), CRP ($p=0.044$), procalcitonin ($p=0.040$) and lactate ($p<0.001$) values of those who died were significantly higher than those who did not die; systolic blood pressure ($p<0.001$), diastolic blood pressure ($p<0.001$), PLT ($p=0.047$), lymphocyte ($p<0.001$), albumin ($p<0.001$), pH ($p<0.001$) and LAI ($p<0.001$) values were significantly lower (Table 1).

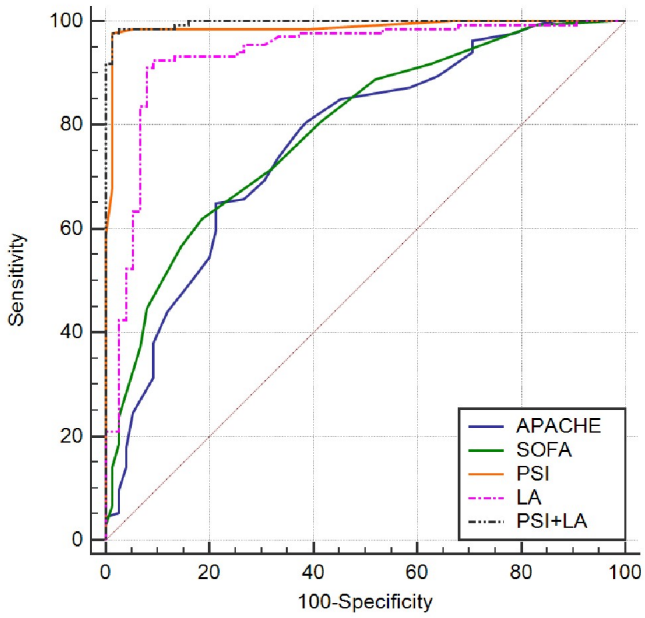

Figure 2. ROC curve analysis of various parameters for mortality

Receiver Operating Characteristic (ROC) curves and cut-off points

ROC analysis investigated the predictive ability of various parameters for mortality in SCAP patients, and cut-off values were determined. For APACHE II (cut-off ≥24), sensitivity and specificity were 64.9% and 78.7%, respectively, indicating good predictive ability. SOFA (cut-off ≥9) also showed good predictive ability with 61.9% sensitivity and 81.3% specificity. PSI (cut-off ≥110) demonstrated excellent predictive power with 97.8% sensitivity and 98.7% specificity. Similarly, LAI (cut-off ≥3379) was a good predictor of mortality, exhibiting 92.5% sensitivity and 90.7% specificity. The AUC values were 0.987 for PSI, 0.933 for LAI, and 0.997 when PSI and LAI were combined (Table 2, Figure 2).

Logistic regression analysis

The logistic regression analysis was performed to evaluate factors that contributed to mortality. Multivariate analysis identified high PSI score, low pulse rate, and LAI value as factors associated with increased mortality risk (Table 3).

Correlation analysis of various parameters

PSI score showed significant positive correlations with APACHE II, SOFA, age, pulse and respiratory rates, CRP, and procalcitonin, and negative correlations with LAI, blood pressure, and albumin. LAI was positively correlated with blood pressure and albumin but negatively with APACHE II, SOFA, age, pulse rate, CRP, and procalcitonin. A positive correlation was observed between APACHE II scores and SOFA scores, age, pulse rate, respiratory rate, and procalcitonin levels. Conversely, APACHE II scores exhibited a negative correlation with systolic blood pressure, diastolic blood pressure, and albumin levels. SOFA was positively correlated with pulse and respiratory rates and procalcitonin and negatively with systolic and diastolic blood pressures and albumin (Table 4).

Discussion

Severe community-acquired pneumonia is a critical infection that often necessitates hospitalization and intensive care support. Early prognosis determination and early management are of lifesaving importance in these patients. This study investigated the importance of both individual and combined use of PSI and LAI in determining patient mortality in the ICU due to SCAP. Our findings suggest that both are highly important in predicting the mortality of SCAP patients and provide a higher success rate when combined.

The PSI score is a comprehensive scoring system including age, comorbidities, vital signs, and laboratory values. Therefore, it provides a broad perspective in assessing the overall condition of patients. Koçak et al. [18] reported that high PSI was associated with low treatment response, prolonged hospital and ICU stay, prolonged treatment duration, and increased mortality rate. In our ROC analysis, we found that a PSI score >110 had a high specificity (98.7%) and sensitivity (97.8%) for predicting mortality in SCAP patients (AUC: 0.987). In particular, the moderate and advanced age groups and comorbidities of the patients may have increased the sensitivity and specificity of the PSI score. However, since the PSI score requires a complex calculation, it may be difficult to use this score in intensive care units due to the high workload of healthcare professionals.

In contrast, the LAI is based on two simple laboratory parameters: lymphocyte count and serum albumin levels. Studies have indicated that lymphopenia is linked to a worse prognosis in infections. Fernandez et al. [19] reported that a lymphocyte count $<724/mm^3$ increased the mortality risk 1.93-fold in patients with SCAP. Albumin levels can serve as an indicator of inflammation severity. Research has shown that serum albumin levels can predict the prognosis of SCAP patients admitted to ICUs [20]. LAI, which is formulated as the product of lymphocyte count and albumin level, is a biomarker that is easier to use in clinical practice to evaluate the severity of inflammatory response. In our study, LAI showed 92.5% sensitivity and 90.7% specificity in predicting mortality with a cut-off value of 3379. These findings reflect previous studies evaluating the prognostic value of LAI, which has been previously reported in different diseases [16, 21-23].

Woo Kim et al. [24] combined procalcitonin or CRP with PSI and IDSA/ATS guidelines in their modeling and observed an increase in the AUC value of adding CRP to PSI and IDAS/ATS in predicting mortality. The primary highlight of our study is that the combination of PSI score and LAI has a significant advantage in predicting mortality. The AUC value of 0.997 was obtained in the ROC analysis. This shows that these two parameters can predict mortality with high accuracy when combined. The PSI score covers a wider range of clinical parameters, whereas the LAI reflects inflammatory status and immune response in a simple but effective way. This situation shows the complementary features of PSI and LAI.

Especially in ICUs, rapid and accurate prognostic evaluation may reduce mortality by providing efficient treatment strategies. Although PSI or LAI alone have a high predictive accuracy, their combined use may improve this accuracy and allow for more reliable management of SCAP patients. The ability of the PSI score to provide a comprehensive assessment, combined with the faster and easier application of the LAI, provides great advantages to clinicians.

The mortality rate was 64.1% in SCAP patients included in our study. This rate is high compared to the literature, and we think that this is due to the high Charlson Comorbidity Index, APACHE II, SOFA, and PSI scores of the patients. We observed that inflammatory parameters such as procalcitonin and CRP were higher in deceased patients, whereas parameters such as lymphocytes and albumin were significantly lower. The need for vasopressors and mechanical ventilation was also significantly higher in these patients. These findings indicate the rapid impairment of organ function in SCAP patients and emphasize the necessity of invasive treatment modalities. We believe that the combination of the LAI and PSI scores may guide the physicians in optimizing the timing of such critical interventions.

Our correlation analysis revealed positive correlations between the PSI score and the Charlson Comorbidity Index, APACHE II, SOFA, age, pulse rate, respiratory rate, CRP, and procalcitonin. This suggests that higher PSI scores are associated with increased disease severity, aligning with these factors. Conversely, LAI showed negative correlations with the Charlson Comorbidity Index, APACHE II, SOFA, age, pulse rate, CRP, and procalcitonin, but a positive correlation with blood pressure. This pattern indicates that this combination of LAI and blood pressure is associated with a poorer prognosis.

Limitations

A notable limitation of this study is that it is retrospective, being conducted at a single center, and limited to

a low sample size, which limits the generalizability of the results. Another limitation is that the data consisted of the initial hospitalization of the patients in intensive care units. Dynamic measurements will provide more reliable data. Our other limitation is that subgroup analysis of microorganisms causing pneumonia was not analyzed. The use of these two scoring systems in different pneumonia subtypes should also be investigated.

Conclusion

This study showed that combining LAI and PSI scores serves as an effective tool for predicting the prognosis of SCAP patients. This combination has the potential to predict mortality early, especially in resource-limited centers or intensive care units with heavy workloads. In intensive care practice, it can both reduce mortality rates by improving clinical decision-making and allow more effective and timely management interventions.

Disclosures

Ethics Committee Approval: Ethical approval was obtained for this study from the Fırat University Non-Interventional Clinical Research Ethics Committee (Document date and number: 27.12.2024-29971).

Informed Consent: Not necessary for this manuscript.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Not necessary for this manuscript.

Financial Disclosure: No funders.

References

1. Torres A, Cillóniz C, Blasi F et al. Burden of pneumococcal community-acquired pneumonia in adults across Europe: A literature review. *Respir Med.* 2018;137:6-13. doi: 10.1016/j.rmed.2018.02.007. Epub 2018 Feb 19. PMID: 29605214.
2. Cillóniz C, Liapikou A, Martin-Loeches I et al. Twenty-year trend in mortality among hospitalized patients with pneumococcal community-acquired pneumonia. *PLoS One.* 2018;13(7):e0200504. doi: 10.1371/journal.pone.0200504. PMID: 30020995.
3. Walden AP, Clarke GM, McKechnie S et al. Patients with community-acquired pneumonia admitted to European intensive care units: an epidemiological survey of the GenOSept cohort. *Critical Care.* 2014;18(2):58–8. doi.org/10.1186/cc13812.
4. Said MA, Johnson HL, Deloria-Knoll M, O´Brien KL. Estimating the Burden of Pneumococcal Pneumonia among Adults: A Systematic Review and Meta-Analysis of Diagnostic Techniques. *PLoS ONE.* 2013; 8:4. doi.org/10.1371/journal.pone.0060273.
5. Prina E, Ranzani OT, Polverino E et al. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. *Ann Am Thorac Soc.* 2015;12(2):153-60. doi: 10.1513/AnnalsATS.201407-305OC. PMID: 25521229.
6. Torres A, Chalmers JD, Dela Cruz CS et al. Challenges in severe community-acquired pneumonia: a point-of-view review. *Intensive Care Med.* 2019;45(2):159-171. doi: 10.1007/s00134-019-05519-y. Epub 2019 Jan 31. PMID: 30706119; PMCID: PMC7094947.
7. Ahn JH, Choi EY. Expanded A-DROP Score: A New Scoring System for the Prediction of Mortality in Hospitalized Patients with Community-acquired Pneumonia. *Sci Rep.* 2018;8(1):14588. doi: 10.1038/s41598-018-32750-2. PMID: 30275523; PMCID: PMC6167349.
8. Boussekey N, Leroy O, Georges H et al. Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in an intensive care unit. *Infection.* 2005;33(4):257-63. doi.org/10.1007/s15010-005-4096-2.
9. Seligman R, Ramos-Lima LF, Oliveira Vdo A et al. Biomarkers in community-acquired pneumonia: a state-of-the-art review. *Clinics (Sao Paulo).* 2012;67(11):1321-5. doi: 10.6061/clinics/2012(11)17. PMID: 23184211; PMCID: PMC3488993.
10. Colak A, Aksit MZ, Toprak B, Yılmaz N. Diagnostic values of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and procalcitonin in early diagnosis of bacteremia. *Turkish Journal of Biochemistry.* 2019;45(1):57-64. doi: 10.1515/tjb-2018-0484.
11. İmre O. Evaluation of Mean Platelet Volüme, Platelet Distribution Width, And Red Cell Distribution Width İn Bipolar Disorder. *Van Med J.* 2023;30(2): 184-192. doi: 10.5505/vtd.2023.14227.
12. Bermejo-Martín JF, Tamayo E, Ruiz G et al. EXPRESS (Expresión Génica en Sepsis) and GRECIA (Grupo de Estudios y Análisis en Cuidados Intensivos) groups. Circulating neutrophil counts and mortality in septic shock. *Critical Care.* 2014;18:1-407. doi: 10.1186/cc13728.
13. Marrie TJ, Lieling WU. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. *Chest.* 2005;127.4: 1260-1270. doi: 10.1378/chest.127.4.1260.
14. Miyazaki H, Nagata N, Akagi T et al. Comprehensive analysis of prognostic factors in hospitalized patients with pneumonia occurring outside hospital: Serum albumin is not less important than pneumonia severity assessment scale. *J Infect Chemother.* 2018;24(8):602-609. doi: 10.1016/j.jiac.2018.03.006. Epub 2018 Apr 5. PMID: 29628384.
15. Ettinger DS, Wood DE, Aisner DL et al Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2022;20(5):497-530. doi: 10.6004/jnccn.2022.0025. PMID: 35545176.
16. Yamamoto T, Kawada K, Hida K et al. Combination of lymphocyte count and albumin concentration as a new prognostic biomarker for rectal cancer. *Sci Rep.* 2021;11(1):5027. doi: 10.1038/s41598-021-84475-4.
17. Zaki HA, Hamdi Alkahlout B, Shaban E et al. The Battle of the Pneumonia Predictors: A Comprehensive Meta-Analysis Comparing the Pneumonia Severity Index (PSI) and the CURB-65 Score in Predicting Mortality and the Need for ICU Support. *Cureus.* 2023;15(7):e42672. doi: 10.7759/cureus.42672. PMID: 37649936; PMCID: PMC10462911.
18. Koçak ND, Uçar MS. Comparison of the Effect of Pneumonia Type and Severity on Follow-up Parameters Using the Pneumonia Severity Index in Inpatients. *Klimik J.* 2013; 26(2):58-63. doi: 10.5152/kd.2013.19.
19. Bermejo-Martin JF, Cilloniz C, Mendez R et al. NEUMONAC Group. Lymphopenic Community Acquired Pneumonia (L-CAP), an Immunological Phenotype Associated with Higher Risk of Mortality. *EBioMedicine.* 2017;24:231–236. doi: 10.1016/j.ebiom.2017.09.023.
20. Magnussen B, Oren Gradel K, Gorm Jensen T et al. Association between Hypoalbuminaemia and Mortality in Patients with Community-Acquired Bacteraemia Is Primarily Related to Acute Disorders. *PLoS One.* 2016;11(9):e0160466. doi: 10.1371/journal.pone.0160466. PMID: 27611431; PMCID: PMC5017704.
21. Yildirim S, Dogan A, Akdag G et al. Novel Prognostic Indicator for Immunotherapy Response: Lymphocyte-to-Albumin (LA) Ratio Predicts Survival in Metastatic NSCLC Patients. *Cancers (Basel).* 2024;16(14):2512. doi: 10.3390/cancers16142512. PMID: 39061152; PMCID: PMC11274503.
22. Wang MD, Duan FF, Hua X et al. A Novel Albumin-Related Nutrition Biomarker Predicts Breast Cancer Prognosis in Neoadjuvant Chemotherapy: A Two-Center Cohort Study. *Nutrients.* 2023;15(19):4292. doi: 10.3390/nu15194292.
23. Heppner B, Untch M, Denkert C et al. Tumor-Infiltrating Lymphocytes: A Predictive and Prognostic Biomarker in Neoadjuvant-Treated HER2-Positive Breast Cancer. *Clin. Cancer Res.* 2016;22(23):5747–5754. doi: 10.1158/1078-0432.CCR-15-2338.
24. Kim MW, Lim JY, Oh SH. Mortality prediction using serum biomarkers and various clinical risk scales in community-acquired pneumonia. *Scand J Clin Lab Invest.* 2017;77(7):486-492. doi: 10.1080/00365513.2017.1344298. Epub 2017 Jul 5. PMID: 28678546.

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Effects of pre-eclampsia on corneal tomography and specular microscopy parameters: A prospective study

Ayna Sariyeva Ismayilov[a,*], Neslihan Parmak Yener[a], Hafize Gokben Ulutas[b], Burcu Dincgez[c]

[a] *University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Ophthalmology, Bursa, Türkiye*
[b] *University of Health Sciences, Bursa City Hospital, Department of Ophthalmology, Bursa, Türkiye*
[c] *University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital, Department of Obstetrics and Gynecology, Bursa, Türkiye*

ARTICLE INFO

Keywords:
Corneal tomography
Intraocular pressure
Preeclampsia
Pregnancy
Specular microscopy

Received: Dec 23, 2024
Accepted: Mar 24, 2025
Available Online: 25.04.2025

DOI:
10.5455/annalsmedres.2024.12.275

Abstract

Aim: To evaluate the effect of preeclampsia on corneal tomography and specular microscopy parameters.

Materials and Methods: A total of 22 preeclamptic women were evaluated prospectively. Patients were evaluated at prepartum and postpartum third months. Best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit lamp, optical coherence tomography, corneal tomography, and specular microscopy were recorded and compared.

Results: Prepartum BCVA was 0.065±0.638 logMAR, and postpartum BCVA was 0.050±0.823 logMAR, which was significantly different (p=0.033). The mean spherical equivalent was -0.68±1.27 diopter at prepartum and 0.00±1.41 diopter at postpartum period (p<0.001). While prepartum IOP was 16.90±2.92 mmHg, post-partum IOP was 15.40±3.17 mmHg (p=0.041). No significant changes were detected between the prepartum and postpartum period in terms of flat keratometry, steep keratometry, average keratometry, max keratometry, topographic astigmatism, and mean corneal endothelial cell density (ECD). The mean ACV (p=0.012), ACD (p=0.035), and ACA (p=0.032), the mean coefficient variation (CV) (p=0.030) were significantly lower at postpartum period (p=0.032). The percentage of hexagonal cells (HEX) increased (p=0.008) at postpartum period. The mean CCT was 572.81±66.79µm in the prepartum period and 553.90±51.51µm in the postpartum period (p=0.039).

Conclusion: This study indicates that preeclampsia affects corneal cell morphology including CV and HEX, and significant changes in BCVA, IOP, and CCT postpartum. Depending on the change in IOP, it may suggest that the ocular hypotensive effect of pregnancy may have been eliminated by preeclampsia. However, no significant differences were found in corneal topography parameters. Further long-term studies with larger patient cohorts are needed to determine whether these effects are persistent and clinically significant.

Introduction

Pregnancy, which is a significant challenge for the woman body, is associated with various physiological and pathological changes. One of the most critical pathologies that can occur during pregnancy is the hypertensive disorders. Hypertensive disorders of pregnancy, affecting nearly 10% of pregnancies, remain the leading cause of perinatal morbidity and fatality worldwide. It can be divided into groups such as chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia. Preeclampsia complicates 3-5% of pregnancies [1]. Preeclampsia is defined as a new onset of hypertension after 20 weeks of gestation accompanied by proteinuria or maternal end-organ disorders in the absence of proteinuria [2]. Eclampsia is characterized by the coexistence of preeclampsia and seizures [3]. Preeclampsia and eclampsia have not only perinatal adverse outcomes but also they are related to future life complications.

Preeclampsia has been claimed to be a multisystemic disorder characterized by blood vessel construction, metabolic disease, endothelial disorder, onset of the coagulation cascade, and activated inflammatory response [4]. It is known that 25% of preeclamptic patients have visual impairment. In severe preeclampsia and eclampsia, there is an increased risk of hypertensive, hemorrhagic, and em-

*Corresponding author:
Email address: myusufova@cu.edu.tr (Ayna Sariyeva Ismayilov)

bolic strokes, presenting with visual symptoms [5]. The most well-known retinal changes in preeclampsia are abnormal retinal vascularity, such as arterio-venous crossing changes, focal vascular narrowing, and generalized attenuation of arterioles. In severe preeclampsia, serous retinal detachment and choroidal infarcts may develop secondary to hypertensive retinopathy [6].

Changes in sex hormones that occur during normal pregnancy affect both the anterior segment and fundus. Previous studies have shown that there are receptors for estrogen, progesterone, and androgen in the nuclei of human corneal epithelial, stromal, and endothelial cells [7-9]. Due to possible fluid retention, corneal thickness and corneal curvature have been reported to increase during pregnancy [10-11]. A recent study has shown higher anterior flat and steep keratometry, central corneal thickness (CCT), corneal volume, anterior chamber depth, angle, and volume, and lower IOP during pregnancy than three months postpartum period [12]. In contrast , another study has reported no statistically significant differences between corneal topographic and biomechanical parameters before pregnancy, during pregnancy, and postpartum. This study showed that prenatal ocular changes returned to fundamental characteristics after the postpartum period [13].

The physiology and hormonal status of preeclampsia pregnant women are quite different from normal pregnants. In preeclampsia, the body's ability to respond to vasoactive agents is initially lost, leading to a reduction in vasoconstriction. This results in a increase in intravascular volume, which then shifts to the extravascular compartments. Furthermore, there is a disruption in the balance between proangiogenic and antiangiogenic factors. Soluble vascular endothelial growth factor (VEGF) and soluble endoglin are two key proangiogenic factors involved in preeclampsia. Additionally, nitric oxide signaling, which is crucial for vascular relaxation, is impaired in this condition [14-15]. We thought that ocular physiology might be affected by existing hormonal changes in preeclampsia, which is a different process from normal pregnancy.

Although anterior segment parameters in pregnant women have been frequently examined in the literature, the effects of preeclampsia have not been investigated. This study prospectively analyzed the impact of preeclampsia on corneal tomography and specular microscopy parameters.

Materials and Methods

This is a prospective, non-interventional and observational study performed at a university-affiliated hospital. The primary endpoint of the study was the change in anterior segment parameters in preeclamptic women after postpartum period. The present study was approved by Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (Protocol number: 2011-KAEK-25 2022/06-18). The study adhered to the principles of the Declaration of Helsinki, and informed consent was obtained from the patients.

A total of 31 patients diagnosed with preeclampsia between July 2022 and July 2023 and hospitalized in the Obstetrics and Gynecology Clinic of Bursa Yuksek Ihtisas Training and Research Hospital were admitted to the study. G*Power software was used for sample size and power analysis. Convenience sampling, a non-probability sampling method, was used in this study. Participants were selected based on their availability and willingness to participate. Preeclampsia was diagnosed in pregnant women with new-onset hypertension (systolic blood pressure (BP) $\geq$ 140 mm Hg and/or diastolic BP $\geq$ 90 mm Hg (twice evaluation at least four hours interval)) after 20 weeks of gestation along with the presence of proteinuria, as defined by one of the following: $\geq$300 mg protein in a 24-hour urine, protein/creatinine ratio $\geq$ 0.3 mg/dL, dipstick protein $\geq$ +2. In the absence of proteinuria, new onset hypertension accompanied by one of the following criteria: thrombocytopenia (platelet count less than 100 000/uL), elevated serum transaminases (twice the upper level of normal), creatinine >1.1 mg/dl, pulmonary edema and/or visual symptoms. If a new-onset tonic-clonic seizure was added to preeclampsia, it was diagnosed as eclampsia [2].

Patients were consulted with the Ophthalmology Clinic at prepartum period and postpartum 3 months. Patients with contact lens use, glaucoma, a history of ocular surgery and trauma, atopy, corneal ectasia, spherical refractive errors of more than 4.00 diopter (D), cylindrical refractive errors of more than 2.00 D, two patients with serous retinal detachment due to preeclampsia having systemic disease such as hypertension, diabetes mellitus, and thyroid disease and patients who do not have regular follow-up were excluded from the study. Finally, a total of 22 patients (44 eyes) were included in the study.

A detailed history and routine ophthalmologic examination were done. Best-corrected visual acuity (BCVA) (Snellen converted to logMAR), intraocular pressure (IOP), slit lamp, dilated fundoscopy, and optical coherence tomography (OCT) (RTVue XR AVANTI, Optovue, Inc., Fremont, CA, USA) were evaluated. The combined Scheimpflug–Placido disc corneal topography system (Sirius, CSO, Florence, Italy) performed the corneal tomography parameters. K1 (flat keratometry), K2 (steep keratometry), Kavg (average keratometry), maximum keratometry (Kmax), anterior chamber volume (ACV), anterior chamber depth (ACD), anterior chamber angle (ACA) were taken. Corneal endothelial cell density (ECD) (cells/ mm^2), polymegathism, hexagonality, and CCT were evaluated automatically using a noncontact specular microscopy (NSP-9900, NonconRobo, Konan, Japan) analyzing at least 100 cells (Figure 1). Evaluations were taken from the central cornea in a suitable head position while the patient sat. Three images were taken, and the best image was recorded for analysis. All measurements were taken during the daytime to prevent diurnal variation (02:00-04.00 PM).

Statistical analysis

Statistical analyses were performed using the SPSS software version 22 (IBM Corp., Armonk, NY, USA). The distribution of variables was tested by using the Shapiro-Wilk test. Continuous, normally distributed data were presented as mean ± standard deviation, while categorical variables were presented as numbers and percentages.

Since the constant data shows normal distribution, the paired sample t-test was performed to compare prepartum and postpartum values. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the patients was 32.22±6.56 (21-42) years. The gestational week was ranged between 20 and 39 weeks. A total of 6 patients (27.2%) were primigravidas, 13 patients (59%) were multigravidas, and 3 patients (13.6%) were grand multiparas. Two patients (9%) were diagnosed with eclampsia while 18 patients (81%8) had mild and 2 patients (9%) had severe preeclampsia.

At the time of ophthalmological examination, mean systolic BP was 149.54±23.39 (120-200), and mean diastolic BP was 88.40±17.68 (60-120) mm Hg. When the symptoms were searched, headache was present in 9 (40.9%) patients, abdominal pain in 2 (9.1%) patients, blurred vision in 8 (36.3%) patients, scotoma in 1 (4.5%) patient, diplopia in 1 (4.5%) patient, transient sudden vision loss in 1 (4.5%) patient and subconjunctival hemorrhage in 2 (9.1%) patients. There was a constriction of retinal arteriole in 6 eyes (13.6%), flame-shaped hemorrhage in 3 (6.8%) eyes, optic disc edema in 2 (4.5%) eyes, cotton-wool spots in 3 (6.8%) eyes, hard exudates in 1 (2.27%) eye.

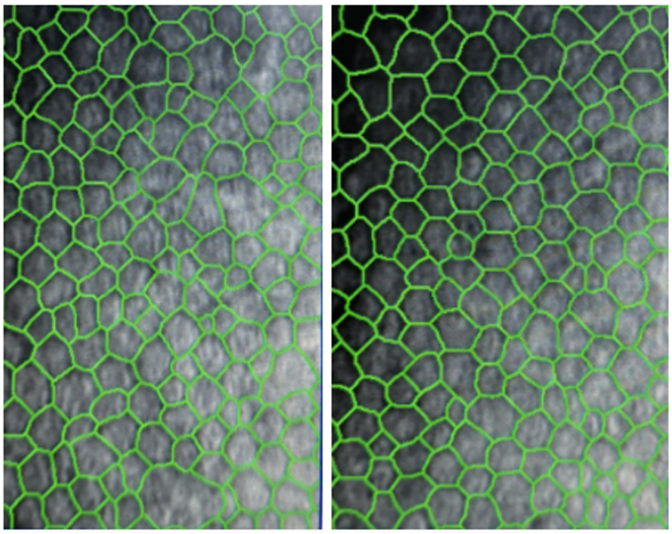

Figure 1. Specular microscopy of a 32-year-old pregnant woman with preeclampsia during the prepartum and postpartum periods.

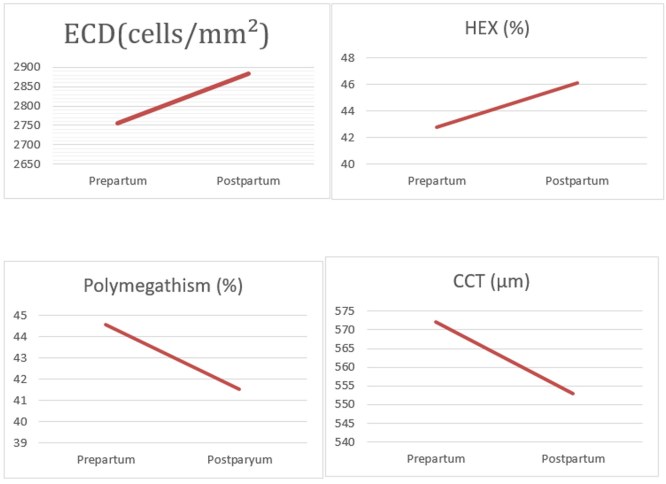

Figure 2. Changes in specular microscopy parameters in the postpartum period.

Table 1. Comparison of corneal tomography parameters in prepartum and postpartum periods.

	Prepartum	Postpartum	
	Average±SD (range)	Average±SD (range)	p value
Flat keratometry (K1) (D)	43.17±1.77 (40.00-46.50)	43.00±1.85 (40.0-46.25)	0.618
Steep keratometry (K2) (D)	44.39±1.92 (41.50-47.50)	44.14±1.93 (41.50-47.50)	0.075
Average keratometry (Kavg) (D)	44.16±1.45 (40.25-47.0)	44.06±1.63 (40.25-47.0)	0.534
Maximum keratometry (Kmax)	46.46±2.28 (44.25-47.75)	45.93±1.62 (44.00-47.75)	0.457
Topographic astigmatism (D)	0.98±2.06 (-2.0-0)	0.94±0.71 (-2.0-0)	0.381
Anterior Chamber Volume (mm^3)	175.45±35.9 (115-252)	164.98±12.4 (121-198)	**0.012***
Anterior Chamber Depth (mm)	3.224±0.765 (2.999-3.987)	2.876±0.355 (2.675-3.654)	**0.035***
Anterior Chamber Angle (°)	42.65±7.91 (29-45)	41.87±5.67 (28-45)	**0.032***

D: Diopter. Paired sample t-test, * p<0.05.

Table 2. Analysis of Endothelial Cell Characteristics in prepartum and postpartum periods.

	Prepartum	Postpartum	
	Average±SD (range)	Average±SD (range)	p value
ECD (cells/mm^2)	2755.47±251.05 (2128-3096)	2883.42±620.90 (2519-3268)	0.125
Polymegathism (CV) (%)	44.57±7.52 (40-59)	41.52±6.61 (29-56)	**0.030***
Pleomorphism (HEX) (%)	42.80±5.43 (39-50)	46.10±5.98 (33-55)	**0.008***
CCT (µm)	572.81±66.79 (408-770)	553.90±51.51 (400-612)	**0.039***

ECD: endothelial cell density, CV: coefficient variation of cell area, HEX: percentage of hexagonal cells, CCT: Central corneal thickness, paired sample t-test, * p<0.05.

Prepartum BCVA was 0.065±0.638 (0-0.698) logMAR, and postpartum BCVA was 0.050±0.823 (0-0.154) logMAR, which was statistically significant (p=0.033). While prepartum IOP was 16.90±2.92 (10-26) mmHg, postpartum IOP was 15.40±3.17 (10-21) (p=0.041). The mean spherical equivalent was -0.68±1.27 (-3.0-2.0) diopter in the prepartum period and 0.00±1.41 (-2.0-3.0) diopter in the postpartum period (p<0.001). Changes in K1, K2, Kavg, Kmax, and topographic astigmatism were not sta-

tistically significant at postpartum period. The mean ACV (p=0.012), ACD (p=0.035), and ACA (p=0.032) decreased statistically significantly at the postpartum third month (Table 1).

The mean ECD values were not statistically significant (p=0.125) between the prepartum and postpartum periods, while the mean CV values decreased (p=0.030) and the mean HEX values increased (p=0.008) significantly after delivery. The mean CCT was 572.81±66.79 µm at the prepartum period and 553.90±51.51 µm at the postpartum period (p=0.039) (Table 2 and Figure 2).

Discussion

Preeclampsia is a multisystem disease secondary to generalized vasoconstriction and endothelial injury. The clinical spectrum of preeclampsia includes hemolysis, low platelets, proteinuria, elevated liver enzymes, and HELLP syndrome [16]. It is well known that preeclampsia causes loss of vision due to changes in the neurological system and retina. The present study evaluated the effects of preeclampsia on the anterior segment. Blurred vision was detected in 36.3% of the preeclamptic patients, and retinal changes due to hypertensive retinopathy were diagnosed in 34%. Postpartum visual acuity increase was found to be statistically significant.

In a study searching IOP in pregnant women, IOP was found to be lower in pregnant women as compared to nonpregnant women [11]. In a study by Atas et al., lower IOP were reported during pregnancy than that the 3-month postpartum period. Moreover, this study claimed higher ACD, ACA, and ACV values during pregnancy as compared to the postpartum period [12]. Similarly, a study searching 25 healthy pregnant women in the second and third trimesters found a significant decline in the IOP and a reciprocal rise in CCT [10]. Since all values returned to the 1st-trimester values at three months postpartum. In the present study, unlike uncomplicated pregnancies, prepartum IOP was higher in preeclamptic pregnancies. The IOPs of the patients decreased significantly by 8.8% after delivery. In addition, it was observed that the ACD, ACA, and ACV measured during pregnancy were greater than in the postpartum period. Although the cause of the reduction in IOP during pregnancy is not fully understood, higher estrogen, progesterone, relaxin, and β-human chorionic gonadotropin levels leading to increased outflow of aqueous humor through the unconventional track are claimed to be the primary mechanism [12,17]. Another possible factor is decreased systemic vascular resistance and episcleral venous pressure. In parallel with this hypothesis, increased systemic vascular resistance in preeclampsia may increase episcleral venous pressure and cause an increase in IOP. Additionally, lower circulating estrogen and progesterone levels in women with preeclampsia may affect the outflow of aqueous humor [18].

Different results exist regarding ACV, ACA, and ACD measurements during pregnancy. Goldich et al. found no difference in ACV, ACD, and ACA measurements between pregnant women in the last trimester and nonpregnant women [11]. Erkan Pota's [19] and Atas's [12] studies reported a significant rise in ACV in the last two trimesters and a reduction in the postpartum period. The present study observed that ACV, ACA, and ACD measurements decreased statistically significantly after delivery.

In this study, we found a hyperopic shift in refractive errors in women with preeclampsia in the postpartum period. The change to hypermetropia may be due to a slight decrease in corneal curvatures. Although lens thickness was not measured in this study, it is known that the lens swells during pregnancy and is a catharogenic process [20]. The hyperopic shift may occur since this situation disappears in the postpartum period. This agrees with Erkan Pota's study [19], which reported that myopia rising to the 3rd trimester and reducting in the postpartum period. Pizzarello et al. [20] reported a tendency to myopia during pregnancy. However, another study showed that refractive measurements were similar in the 3rd trimester and postpartum period [12].

Some studies have reported that estrogen, progesterone, and androgen receptors exist in human corneal epithelial, stromal, and endothelial cell nuclei [7-9]. Hormonal changes during pregnancy can cause corneal curvature steepening and increased CCT [10,21,22]. Consistent with the literature, we found higher CCT values in pregnant women with preeclampsia at prepartum period. A study reported a significant decrease in K2, while no statistical changes were present in K1 and Kmean at the postpartum period [19]. In some studies [10,17], no significant alterations in keratometry parameters were observed due to pregnancy. The present study demonstrated that flat keratometry, steep keratometry, and average and maximum keratometry values did not significantly change in the postpartum period as compared to the prepartum period.

The most essential function of the corneal endothelium is to supply corneal transparency. It ensures the balance between the flow of aqueous humor into the stroma and the pumping of aqueous humor into the anterior chamber. The age-related decrease in ECD is compensated by increased Na, K-ATPase activity, which is the basis of endothelial pump function [23]. Corneal endothelial self-renewal is very limited, and the healthy indicators are higher ECD and HEX and lower polymegatism (CV) [24]. In this study, the mean ECD value changes were not statistically significant, but the mean CV and CCT values decreased, and the mean HEX values increased significantly at postpartum period. It is unclear why the transient high CV and low HEX values were measured in pregnant women with preeclampsia. We speculate that this may be due to general inflammation in the preeclampsia. In preeclampsia, placental oxidative stress appears because there is insufficient blood flow to the placenta. This results in the excess release of soluble fms-like tyrosine kinase-1 (sFlt-1), the soluble receptor for vascular endothelial growth factor (VEGF), into the maternal circulation, triggering an inflammatory response and endothelial dysfunction [25]. Monocyte and granulocyte activity and proinflammatory cytokines TNF-alpha, IL-6, and soluble phospholipase A2 increase in circulation [26,27]. It is known that anterior chamber inflammation results in alterations to the shape and size of the cells and a decrease in ECD [28]. Lower ECDs are associated with higher levels of specific cytokines, including IL-1α, IL-4, IL-13, MIP-1β, TNF-α, and

E-selectin [29]. Systemic inflammation during preeclampsia may have caused increased levels of cytokines in the aqueous humor and morphologically affected endothelial cells or endothelial cells may have been exposed to hypoxia during this inflammatory process. Although a study reported that the ophthalmic microenvironment continues immune concession by manipulating local innate and adaptive immunity far from inflammatory responses [30], it has also been shown that severe systemic hypertension in animals increases NADPH oxidase activity and reactive oxygen radicals in the cornea [31].

The present study has some limitations. The number of participants was small, there was the absence of a normal pregnant group, a single eye examination was performed before and after delivery, not measuring axial length and lens thickness, the patients' systemic BP was not recorded at the postpartum period, and the correlation between blood pressure and ocular measurements could not have been determined. The majority of the patient group were mild preeclampsia cases. Patients with retinal changes, except for serous retinal detachment due to preeclampsia, were included.

Conclusion

In conclusion, this study indicates that preeclampsia affects corneal cell morphology including CV and HEX, and significant changes in BCVA, IOP, and CCT postpartum. The ocular hypotensive effects of pregnancy may be eliminated by preeclampsia due to the increase in systemic vascular pressure, which can affect episcleral venous pressure. Alternatively, unlike in normal pregnancies, in preeclampsia the reduced levels of estrogen and progesterone may impair aqueous outflow. In addition, no significant differences were found in corneal topography parameters. Further long-term studies with larger patient cohorts are needed to determine whether these effects are persistent and clinically significant.

Disclosures

Ethics Committee Approval: The present study was approved by Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (Protocol number: 2011-KAEK-25 2022/06-18).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: ASI, BD; Design: ASI, HGU; Supervision: NPY, BD; Materials: ASI, NPY, HGU, BD; Data Collection and/or Processing: ASI, NPY, HGU, BD; Analysis and Interpretation: ASI; Literature Review: ASI, NPY, HGU; Writing Manuscript: ASI, BD; Critical Review: ASI, BD.

Conflict of Interest: None of the authors have any potential conflicts of interest to disclose.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Ananth CV, Keyes KM, Wapner RJ. Pre-Eclampsia Rates in the United States, 1980–2010: Age-Period-Cohort Analysis. *BMJ.* 2013;347:f6564. https://doi.org/10.1136/bmj.f6564.
2. American College of Obstetrics and Gynecology (ACOG): ACOG Practice Bulletin, Number 222: Gestational Hypertension and Preeclampsia, *Obstet Gynecol.* 2020;135(6):e237-60. https://doi.org/10.1097/aog.0000000000003891.
3. National Guideline Alliance (UK) Hypertension in Pregnancy: Diagnosis and Management (NG133);2019 Available online: https://www.nice.org.uk/guidance/ng133.
4. Roberts JM, Pearson G, Cutler J, Lindheimer M. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. *Hypertension.* 2003;41(3):437–445. https://doi.org/10.1161/01.hyp.0000054981.03589.e9.
5. Gilbert AL, Prasad S, Mallery RM. Neuro-ophthalmic disorders in pregnancy. *Neurol. Clin.* 2019; 37(1):85–102. https://doi.org/10.1016/j.ncl.2018.09.001.
6. Practice Bulletin No. 222: Gestational hypertension and preeclampsia. *Am Coll Obstet Gynecol.* 2020;135(6):e237–60. https://doi.org/10.1097/aog.0000000000003891.
7. Gupta PD, Johar K, Nagpal K, Vasavada AR. Sex hormone receptors in the human eye. Surv. Ophthalmol. 2005;50(3):274–284. https://doi.org/10.1016/j.survophthal.2005.02.005.
8. Suzuki T, Kinoshita Y, Tachibana M, Matsushima Y, Kobayashi Y, Adachi et al. Expression of sex steroid hormone receptors in human cornea. *Curr Eye Res.* 2001;22(1):28–33. https://doi.org/10.1076/ceyr.22.1.28.6980.
9. Wickham LA, Gao J, Toda I, Rocha EM, Ona M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. *Acta Ophthalmol Scand.* 2000;78(2):146–153. https://doi.org/10.1034/j.1600-0420.2000.078002146.x.
10. Efe YK, Ugurbas SC, Alpay A, Ugurbas SH. The course of corneal and intraocular pressure changes during pregnancy. *Can. J. Ophthalmol.* 2012;47(2):150–154. https://doi.org/10.1016/j.jcjo.2012.01.004.
11. Goldich Y, Cooper M, Barkana Y, Tovbin J, Ovadia KL, Avni I, et al. Ocular anterior segment changes in pregnancy. *J. Cataract. Refract. Surg.* 2014;40(11):1868–1871. https://doi.org/10.1016/j.jcrs.2014.02.042.
12. Ataş M, Duru N, Ulusoy DM, Altınparmak H, Duru Z, Açmaz G, et al. Evaluation of anterior segment parameters during and after pregnancy. *Cont. Lens. Anterior. Eye.* 2014;37(6):447–450. https://doi.org/10.1016/j.clae.2014.07.013.
13. Naderan M, Jahanrad A. Anterior, posterior and biomechanical parameters of cornea during pregnancy in healthy eyes: a cohort study. *The British journal of ophthalmology.* 2018;102(3):309–312. https://doi.org/10.1136/bjophthalmol-2017-310247.
14. Dieckman WJ. The toxemias of pregnancy. 2nd ed. Mosby; *St Lousi.* 1952; 240-249.
15. Sunness JS. The pregnant woman's eye. *Surv Ophthalmol.* 1988;32(4):219-238. https://doi.org/10.1016/0039-6257(88)90172-5.
16. 1Kongwattanakul K, Saksiriwuttho P, Chaiyarach S, Thepsuthammarat K. Incidence, characteristics, maternal complications, and perinatal outcomes associated with preeclampsia with severe features and HELPP syndrome. *Int. J. Womens. Health.* 2018;10:371–377. https://doi.org/10.2147/ijwh.s168569.
17. Taradaj K, Ginda T, Ciechanowicz P, Maciejewicz P, Suchońska B, Szymusik I, et al. Changes in the parameters of the anterior segment of the eye in pregnant women—literature review. *Ginekol. Pol.* 2018;89(3):169–173. https://doi.org/10.5603/gp.a2018.0028.
18. Wan J, Hu Z, Zeng K, Yin Y, Zhao M, Chen M, et al. The reduction in circulating levels of estrogen and progesterone in women with preeclampsia. *Pregnancy Hypertension.* 2018;11:18-25. https://doi.org/10.1016/j.preghy.2017.12.003.
19. Erkan Pota Ç, Çetinkaya Yaprak A. Evaluation of anterior segment parameters between pregnancy trimesters and postpartum with pentacam scheimflug ımaging: a prospective study. *International ophthalmology.* 2024;44(1):268. https://doi.org/10.1007/s10792-024-03173-y.
20. Pizzarello LD. Refractive changes in pregnancy. Graefes Arch. Clin. Exp. *Ophthalmol.* 2003; 241(6):484–488. https://doi.org/10.1007/s00417-003-0674-0.
21. Spoerl E, Zubaty V, Raiskup-Wolf F, Pillınat LE. Oestrogen-induced changes in biomechanics in the cornea as a possible reason for keratectasia. *Br. J. Ophthalmol.* 2007;91(11):1547–50. https://doi.org/10.1136/bjo.2007.124388.

22. Bilgihan K, Hondur A, Sul S, Ozturk S. Pregnancy-induced progression of keratoconus. *Cornea.* 2011;30(9):991–994. https://doi.org/10.1097/ico.0b013e3182068adc.
23. Watsky MA, McDermott ML, Edelhauser HF. In vitro corneal endothelial permeability in rabbit and human: the effects of age, cataract surgery and diabetes. *Exp. Eye. Res.* 1989;49(5):751–67. https://doi.org/10.1016/s0014-4835(89)80036-3.
24. Garza-Leon, M. Corneal endothelial cell analysis using two non-contact specular microscopes in healthy subjects. *Int. Ophthalmol.* 2016;36(4):453-461. https://doi.org/10.1007/s10792-015-0133-z.
25. Borzychowski A, Sargent I, Redman C. Inflammation and pre-eclampsia. *Seminars in Fetal and Neonatal Medicine.* 2006;11(5):309-316. https://doi.org/10.1016/j.siny.2006.04.001.
26. Vince GS, Starkey PM, Austgulen R, Kwiatkowski D, Redman CW. Interleukin-6, tumor necrosis factor, and soluble tumor necrosis factor receptors in women with pre-eclampsia. *Br J Obstet Gynaecol.* 1995;102(1):20-25. https://doi.org/10.1111/j.1471-0528.1995.tb09020.x.
27. Lim KH, Rice GE, de Groot CJ, Taylor RN. Plasma type II phospholipase A2 levels are elevated in severe preeclampsia. *American journal of obstetrics and gynecology.* 1995;172(3):998-1002. https://doi.org/10.1016/0002-9378(95)90033-0.
28. Alfawaz AM, Holland GN, Yu F, Margolis MS, Giaconi JA, Aldave AJ. Corneal endothelium in patients with anterior uveitis. *Ophthalmol.* 2016;123(8):1637-1645. https://doi.org/10.1016/j.ophtha.2016.04.036.
29. Yamaguchi T, Higa K, Suzuki T, Aketa N, Dogru M, Satake Y, et al. Association between corneal endothelial cell densities and elevated cytokine levels in the aqueous humor. *Scientific Reports.* 2017;7(1):1-8. https://doi.org/10.1038/s41598-017-14131-3.
30. Taylor AW. A review of the influence of aqueous humor on immunity. *Ocular Immunology and Inflammation.* 2003;11(4):231–241. https://doi.org/10.1076/ocii.11.4.231.18269.
31. Santana-Garrido Á, Reyes-Goya C, Arroyo-Barrios A, André H, Vázquez CM, Mate A. Hypertension secondary to nitric oxide depletion produces oxidative imbalance and inflammatory/fibrotic outcomes in the cornea of C57BL/6 mice. *J. Physiol. Biochem.* 2022;78(4):915-932. https://doi.org/10.1007/s13105-022-00916-2.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Anatomic variations of the gastrocolic trunk of Henle and implications for colon surgery

Ergin Erginoz[a,*], Ahmet Necati Sanli[b], Seda Aladag Kurt[c], Muratcan Firat[a], Fatma Guler Yildirim[a]

[a]*Istanbul University–Cerrahpasa, Cerrahpasa Medical Faculty, Department of Anatomy, Istanbul, Türkiye*
[b]*Istanbul University–Cerrahpasa, Cerrahpasa Medical Faculty, Department of General Surgery, Istanbul, Türkiye*
[c]*Istanbul University–Cerrahpasa, Cerrahpasa Medical Faculty, Department of Radiology, Istanbul, Türkiye*

ARTICLE INFO

Keywords:
Gastrocolic trunk
Gastropancreaticocolic trunk
Henle's trunk
Colon cancer
Gastric cancer

Received: Jan 03, 2025
Accepted: Apr 10, 2025
Available Online: 25.04.2025

DOI:
10.5455/annalsmedres.2024.12.286

Abstract

Aim: Henle's trunk is a crucial venous structure involved in the drainage of veins originating from the stomach, colon, and the pancreas. Variations in the formation of the trunk exist and it can have significant clinical implications, particularly in procedures involving lymphadenectomy and vessel ligation around this location. In this study, we aimed to demonstrate variations in the venous architecture of the Henle's trunk with the use of CT images.

Materials and Methods: In this retrospective study, 287 patients who had 3D CT imaging for different purposes in a single institution between January 2018 and June 2022 were evaluated. Patients were grouped into two groups as gastrocolic trunk and gastropancreaticocolic trunk based on the presence of a pancreatic branch contributing to the formation of Henle's trunk. Variations in these two groups were retrospectively evaluated.

Results: Variations of the Henle's trunk are classified as bipod, tripod, or tetrapod. In our series (n=287), the most common subclassification of the gastrocolic trunk was a bipod which included right gastroepiploic vein and right colic vein (n=36, 12.5%). The most common subclassification of the gastropancreaticocolic trunk was a tripod which included right gastroepiploic vein, right colic vein, and anterior superior pancreaticoduodenal vein (n=80, 60.6%).

Conclusion: A thorough examination of the right colon vascular anatomy requires an understanding of venous variations of the Henle's trunk. These variations highlight the importance of individualized assessments for patients, especially those undergoing right hemicolectomy and gastrectomy. This knowledge will aid in reducing surgical complications and improving oncologic outcomes.

Introduction

The venous vascular structure of the right colon is intricate and frequently differs from that of the left side. Regarding oncologic surgery, this complex variation in the vascular structure makes lymph node dissection quite difficult around this anatomical location [1]. Furthermore, severe bleeding may arise during surgery from rupture of the delicate tributaries of the superior mesenteric vein (SMV), particularly the branches of the Henle's trunk, due to improper traction during surgery [1].

Henle originally introduced the idea of the gastrocolic venous trunk in 1868 [2]. This venous trunk, also known as the gastrocolic trunk, consists of venous supply from the stomach (right gastroepiploic vein) and the colon (middle colic vein, right colic vein, or the superior right colic vein). Various studies have also included a pancreatic branch (anterior superior pancreaticoduodenal vein) entering the trunk and renamed the trunk as gastropancreaticocolic trunk [1,3,4]. This new definition made the Henle's trunk form by three veins.

Henle's trunk becomes clinically important during complete mesocolic excision (CME) in right-sided colon surgery. Hohenberger was the first to introduce the concept of CME with central vascular ligation [5]. According to this concept, performing CME with central vascular ligation removes the most centrally draining nodes that may contain metastases [1,5]. It is, therefore, essential to understand the normal pattern as well as the variations of venous structures to minimize complications during surgery

*Corresponding author:
Email address: eerginoz@ku.edu.tr (Ergin Erginoz)

as well as to perform proper lymphadenectomy.

The purpose of this study is to present variations of the venous anatomy of the gastropancreaticocolic trunk of Henle in patients using 3D computerized tomography (CT) imaging.

Materials and Methods

This retrospective study included 287 patients who underwent 3D CT imaging for various indications in a single institution between January 2018 and June 2022. Patients with a history of bowel perforation, abdominal radiation history, colon cancer (and colon surgery), and inadequate evaluation of the CT images were excluded from the study since the vascular anatomy may be altered (i.e., neovascularization) or resected in the presence of a surgical history. The vascular structures forming the Henle's trunk such as the right gastroepiploic vein (RGEV), middle colic vein (MCV), accessory middle colic vein (aMCV), right colic vein (RCV), superior right colic vein (sRCV), and anterior superior pancreaticoduodenal vein (ASPDV) were evaluated using dynamic abdominal CT images using our local PACS archive system. In our study, we have used the subclassification of Henle's trunk discussed by Gao et al. and categorized it into two groups based on the involvement of the pancreatic branch [3].

Type I only included the gastric and colic branches. In type Ia, RGEV and RCV formed the trunk while in type Ib, RGEV and SRCV formed the trunk. In type Ic, RGEV, RCV, and SRCV formed a tripod and the common trunk drained into the superior mesenteric vein. In type Id, RGEV and MCV together drained into the trunk while an accessory middle colic vein was present in type Ie, forming a tripod.

The type II included gastric, colic, and pancreatic branches. In type IIa, RGEV, RCV, and ASPDV formed the trunk while in type IIb, RGEV, SRCV, and ASPDV formed the trunk. In type IIc, a superior right colic vein was present besides the right colic vein, forming a tetrapod venous structure draining into the trunk. In type IId, RGEV, MCV, and ASPDV formed a tripod while in type IIe, RGEV, MCV, aMCV, and ASPDV formed the trunk. The variations observed in our study are shown in Figure 1.

The venous tributaries that formed the Henle's trunk were analyzed using the portal venous phase. The computerized tomography images were evaluated in three different orthogonal views and sometimes a 3D structure was created for clarity.

Each patient was examined by a dual-course CT scanner in triphasic imaging, including hepatic arterial, portal venous, and hepatic venous phases. Two dual-source CT scanners were used: SOMATOM Definition AS (Siemens Healthcare, Forchheim, Germany) and Revolution CT (GE Healthcare, Milwaukee, Wisconsin). The scanning parameters were as follows: 120–140 kV tube voltage with min 140 mA–max 400 mA using automatic tube current modulation, pitch 1, matrix 512×512, slice thickness of 5 mm with 1.25 reconstruction. For 3D reconstruction, the volume rendering techniques was used by Siemens syngo.via software and the GE AW server. Also various, post-processing software (SAFIRE, ASiR-V) were automatically used for dose modulation.

The study was performed in accordance with the ethics guidelines of the Helsinki Declaration and was approved by the local ethics committee (Istanbul University-Cerrahpaşa Clinical Research Ethics Committee, approval number: E–83045809–604.01–1118237).

Results

Among the patients involved in the study (n=287), 154 were male (53.6%) and 133 were female (46.4%). The average age of the individuals was 51.17 ± 12 (age range 21–76). Among the gastrocolic trunk (n=81, type I), the most common type was type Ia with 36 patients (12.5%) (Table 1). This subtype included the right gastroepiploic vein forming a trunk with the right colic vein (Figure 2). The occurrence was followed by type Ib with 22 patients (7.7%), type Id with 17 patients (5.9%), type Ic with 4 patients (1.4%), and type Ie with 2 patients (0.7%). As observed in type Ie, an additional middle colic vein was referred to as the accessory middle colic vein.

Among the gastropancreaticocolic trunk (n=174, type II), the most commonly observed subtype was type IIa with 80 patients (27.9%) (Table 2). This subtype included the right gastroepiploic vein forming a tripod with the right colic vein and anterior superior pancreaticoduodenal vein (Figure 3). This was followed by type IIb with 36 patients (12.5%), type IId with 33 patients (11.5%), type IIc with 23 patients (8%), and type IIe with 2 patients (0.7%). Similar to type Ie, an additional middle colic vein was

Table 1. Gastrocolic subclassification of the Henle trunk based on the venous tributaries from the right colon.

Type of Henle trunk	Venous drainage	Frequency, n (%)
I		81 (28.2)
Ia	RGEV + RCV	36 (12.5)
Ib	RGEV + SRCV	22 (7.7)
Ic	RGEV + RCV + SRCV	4 (1.4)
Id	RGEV + MCV	17 (5.9)
Ie	RGEV + MCV + aMCV	2 (0.7)

RGEV: right gastroepiploic vein; RCV: right colic vein; SRCV: superior right colic vein; MCV: middle colic vein; aMCV: accessory middle colic vein.

Table 2. Gastropancreaticocolic subclassification of the Henle trunk based on the venous tributaries from the right colon.

Type of Henle trunk	Venous drainage	Frequency n (%)
II		174 (60.6)
IIa	RGEV + ASPDV + RCV	80 (27.9)
IIb	RGEV + ASPDV + SRCV	36 (12.5)
IIc	RGEV + ASPDV + RCV + SRCV	23 (8.0)
IId	RGEV + ASPDV + MCV	33 (11.5)
IIe	RGEV + ASPDV + MCV + aMCV	2 (0.7)

RGEV: right gastroepiploic vein; RCV: right colic vein; SRCV: superior right colic vein; MCV: middle colic vein; ASPDV: anterior superior pancreaticoduodenal vein; aMCV: accessory middle colic vein.

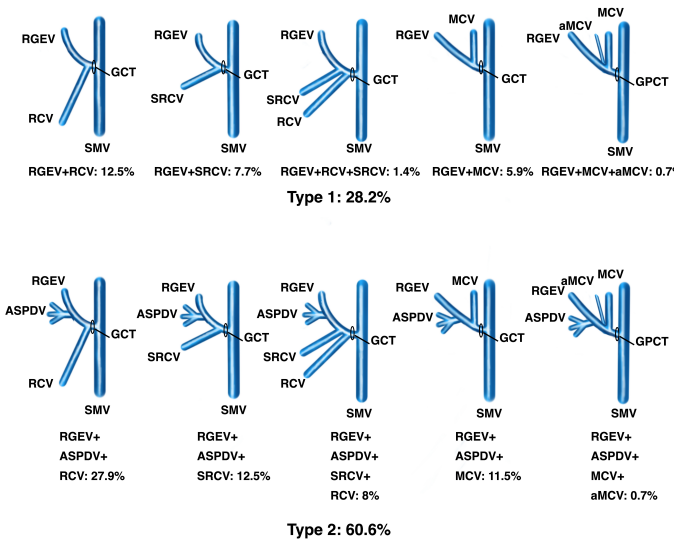

Figure 1. The venous tributaries that lead to the formation of gastrocolic (type 1) and gastropancreaticocolic (type 2) trunks.

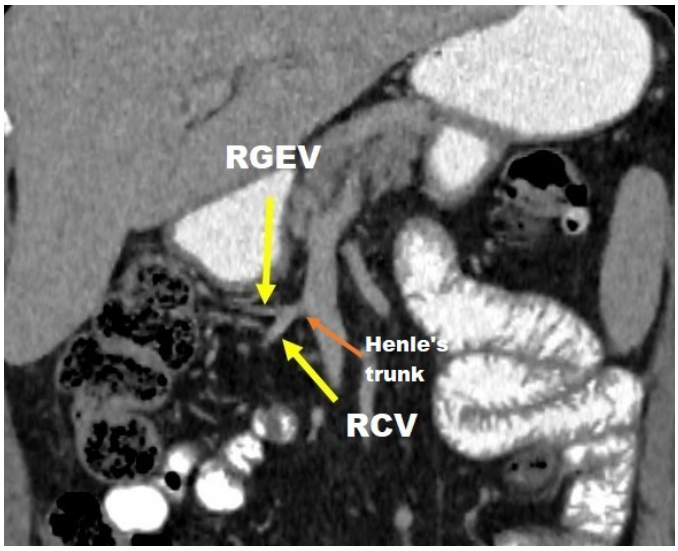

Figure 2. The RGEV and RCV forming the most commonly observed gastrocolic trunk of Henle.

referred to as the accessory middle colic vein in type IIe. We did not observe three middle colic veins in any of our patients included in the study.

In 32 patients (11.1%), there were no colic tributaries and the trunk was only formed between gastric and pancreatic branches. Since the gastropancreaticocolic trunk and the formerly known gastrocolic trunk always included a colic branch, this group did not include a colic branch and because of this reason they were referred to as the unclassifiable group. Among this group, the RGEV and ASPDV formed a common trunk before draining into the superior mesenteric vein.

Discussion

Following the principles of total mesorectal excision in rectal cancer, complete mesocolic excision was introduced by Hohenberger et al. in 1992 which revolutionized colon cancer surgery and patient oncologic outcomes [5–7]. CME involves isolation of the visceral fascia, dissection of lymph

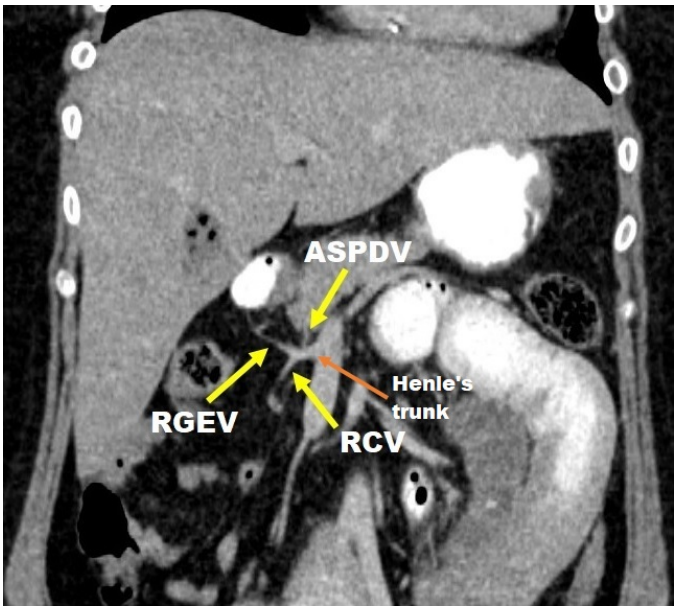

Figure 3. The RGEV, RCV, and ASPDV forming the most commonly observed gastropancreaticocolic trunk of Henle.

nodes around the origin of the mesenteric arteries, and central (high) ligation of the arteries [3,8,9]. Performing complete mesocolic excision with central vascular ligation and obtaining negative surgical resection margins by preserving the embryological planes are the essential factors that determine the oncologic outcome of the patient [1]. For this reason, understanding the normal anatomy and the variations of the venous supply is important during right colon cancer surgery. This study provides information about the formation of the Henle trunk and presents vascular variations among different individuals.

Although Henle first described the gastrocolic trunk in 1868, Descomps et al. observed an additional vein that formed the gastrocolic trunk, namely ASPDV [10]. Ever since, various cadaveric and radiological studies have been published that presented their findings. Variations of the Henle's trunk in the literature are often classified as bipod, tripod, or tetrapod. When defining vein tributaries, when more than two right colic veins or middle colic veins are present, the thicker vein is defined as the main vein whereas the thinner vein is defined as the accessory vein [3].

Cadaveric studies on the variations of Henle's trunk have yielded different results. In the majority of the studies, Henle's trunk was formed between RGEV, ASPDV, and a colic vein (gastropancreaticocolic trunk). Kuzu et al. have studied 111 cadavers with a 78.4% incidence of gastropancreaticocolic trunk. This trunk was most commonly formed between RGEV, ASPDV, and RCV (41.4%) [1]. This finding was similar to our results. Jin et al. dissected 9 cadavers with the most common observation (50%) of RGEV, ASPDV, SRCV, and RCV forming the Henle's trunk [11]. On the other hand, Yamaguchi et al. studied 58 cadavers and observed RGEV, ASPDV, and aMCV forming the Henle's trunk most commonly (55%) [12]. In their findings, the gastrocolic trunk was absent in 31% of the cadavers. Ignjatovic et al. have dissected 34 cadavers and the most common tributaries of the Henle's

trunk (73.5%) were RGEV, SRCV, and ADPDV or anterior inferior pancreaticoduodenal vein [13]. Stefura et al. performed a meta-analysis on the prevalence of tributary variations of Henle's trunk [14]. Among the studies, they found that the most common venous variation forming the Henle's trunk was RGEV, SRCV, and ASPDV ($p<0.01$) [14].

Besides cadaveric studies, the prevalence of Henle's trunk was also studied with 3D CT images. Usually, these studies involved a larger number of patients simply due to the simplicity of observing radiological images. Sakaguchi et al. studied 102 patients where 79 had Henle's trunk (77.5%) [15]. The most common venous tributaries that formed the Henle's trunk were RGEV and SRCV (53.2%). The least common was RGEV and RCV (1.3%). It was important, however, to note that ASPDV was not observed in any of the cases. In another study, Ogino et al. observed 87.7% of Henle's trunk in a total of 81 patients [16]. The most commonly observed variation was RGEV, ASPDV, and RCV, which was similar to our findings. The least common variation was RGEV, ASPDV, and MCV. Our study included an occurrence of Henle's trunk in 88.8% of the cases (n=287). RGEV and RCV was the most common type that formed the gastrocolic trunk of Henle while RGEV, ASPDV, and RCV were the most common type that formed the gastropancreaticocolic trunk of Henle. The least commonly observed gastrocolic trunk subtype was RGEV, MCV, and aMCV while the least commonly observed gastropancreaticocolic trunk subtype was RGEV, ASPDV, MCV, and Amcv in our series.

Henle's trunk becomes important not only in colon surgery but also in gastric surgery. The RGEV is present in almost all types of variations of Henle's trunk as mentioned in previously. It is therefore essential to observe its course to ligate the vessel and perform proper lymphadenectomy. According to the Japanese Gastric Cancer Association, the lymph nodes inferior to the pyloric region are numbered as the number 6 lymph node station [17]. Patients with gastric cancer display metastasis to number 6 lymph nodes at a rate between 3.95–34% [3,18–22]. Due to this rate, it is necessary to remove the number 6 lymph nodes during radical gastrectomy [23–25]. The RGEV displays various drainage patterns under the head of the pancreas. Therefore, understanding the anatomical confluence of the RGEV is essential to perform proper oncologic dissection of the number 6 lymph node [22].

Another important colic tributary that form the Henle's trunk is the middle colic vein. In our study, middle colic vein were identified in all patients. Based on the data from Tables 1 and 2, in only 18.8% of the patients the middle colic vein drained into the Henle's trunk while 81.2% drained into the SMV. Maki et al. studied the variations of the middle colic vein in 3D CT angiography images [26]. According to their results, MCV was present in all patients and the MCVs drained into the SMV in 62.5% of patients, gastrocolic trunk in 29.3% of patients, inferior mesenteric vein in 4.8% of patients, splenic vein in 2.7% of patients and jejunal vein in 0.6% of patients [26].

One important limitation of this research is the radiologic nature of the study. The gastrocolic trunk of Henle has been renamed as gastropancreaticocolic trunk of Henle simply due to the observation of the presence of ASPDV. Many cadaveric studies mentioned earlier included this thin, delicate venous structure as part of the dissection. In radiologic 3D CT images, however, thin, small vessels such as ASPDV or the accessory MCV may be easily missed if the imaging modality is of bad quality. Small vessels may be missed due to motion artifacts, limited spatial resolution, low contrast enhancement, or inadequate temporal resolution. For this reason, patients with CT images that did not have adequate quality for venous structure visualization were excluded from the study.

The clinical importance of the Henle's trunk became more prominent with the introduction of complete mesocolic excision (CME) in colon surgery. In CME, the mesocolic plane is protected and the supplying arteries are highly ligated, which resulted in improved patient survival outcomes and decreased local recurrence rates. During CME of the right colon, the right colon must be freely mobilized to perform adequate lymphadenectomy. Due to the anatomical landmark of the Henle's trunk, misrecognition of the vessels can lead to uncontrollable bleeding during surgery. Hohenberger referred to this point as the "bleeding point" during right-sided CME surgery [5].

There also seems to be a lack of standardization in categorizing Henle's trunk. Because of this, we decided to group Henle's trunk into two categories based on the presence of the pancreatic vein tributary. A consensus may be reached in standardizing the subtypes of Henle's trunk and further research may be conducted to measure the quantitative values (such as the length and diameter of vessels) and the proximity of arterial and venous structures within the mesocolon.

Conclusion

Understanding the venous variations of the Henle's trunk is crucial for a comprehensive review of the vascular anatomy of the colon. The variability in its anatomy emphasizes the need for detailed knowledge during colectomy and gastrectomy in order to minimize complications and to achieve proper lymphadenectomy for better oncologic outcomes.

Disclosures

Ethics Committee Approval: Ethical approval was obtained for this study from the Istanbul University-Cerrahpaşa Clinical Research Ethics Committee (approval number: E–83045809–604.01–1118237).

Informed Consent: Not necessary for this manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: EE, FGY; Design: EE, ANŞ, FGY; Supervision: SAK, FGY; Materials: EE; Data Collection: EE, ANŞ, SAK; Analysis: EE, MF, Literature Review: EE, ANŞ; Writing: EE, SAK, MF; Critical Review: SAK, MF, FGY.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: None.

References

1. Kuzu MA, İsmail E, Çelik S, et al. Variations in the Vascular Anatomy of the Right Colon and Implications for Right-Sided Colon Surgery. *Dis Colon Rectum.* 2017;60(3):290-298. doi: 10.1097/DCR.0000000000000777.
2. Henle J. Handbuch der systematischen anatomie des menschen. III. 1, in Handbuch der gefaesslehre des menschen note 1, p. 371, Friedrich vieweg und sohn, Braunschweig, Germany, 1968.
3. Gao Y, Lu Y. Variations of Gastrocolic Trunk of Henle and Its Significance in Gastrocolic Surgery. *Gastroenterol Res Pract.* 2018;2018:3573680. doi: 10.1155/2018/3573680.
4. Wu C, Ye K, Wu Y, et al. Variations in right colic vascular anatomy observed during laparoscopic right colectomy. *World J Surg Oncol.* 2019;17(1):16. doi: 10.1186/s12957-019-1561-4.
5. Hohenberger W, Weber K, Matzel K, et al. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation - Technical notes and outcome. *Color Dis.* 2009;11(4):354–64. doi: 10.1111/j.1463-1318.2008.01735.x.
6. Lu JY, Xu L, Xue HD, et al. The Radical Extent of lymphadenectomy - D2 dissection versus complete mesocolic excision of LAparoscopic Right Colectomy for right-sided colon cancer (RELARC) trial: study protocol for a randomized controlled trial. *Trials.* 2016;17(1):582. doi: 10.1186/s13063-016-1710-9.
7. Killeen S, Mannion M, Devaney A, Winter DC. Complete mesocolic resection and extended lymphadenectomy for colon cancer: a systematic review. *Colorectal Dis.* 2014;16(8):577-94. doi: 10.1111/codi.12616.
8. Bertelsen CA. Complete mesocolic excision an assessment of feasibility and outcome. *Dan Med J.* 2017;64(2):B5334. PMID: 28157065.
9. Gouvas N, Agalianos C, Papaparaskeva K, et al. Surgery along the embryological planes for colon cancer: a systematic review of complete mesocolic excision. *Int J Colorectal Dis.* 2016;31(9):1577–1594. doi: 10.1007/s00384-016-2626-2.
10. Descomps P, Lalaubie G. Les veines mésentériques. *Journal De Lanatomie Et De La Physiologie Normales Et Pathologiques De Lhomme Et Des Animaux.* 1912;48:337–376.
11. Jin G, Tuo H, Sugiyama M, et al. Anatomic study of the superior right colic vein: its relevance to pancreatic and colonic surgery. *Am J Surg.* 2006;191(1):100-3. doi: 10.1016/j.amjsurg.2005.10.009.
12. Yamaguchi S, Kuroyanagi H, Milsom JW, Sim R, Shimada H. Venous anatomy of the right colon: precise structure of the major veins and gastrocolic trunk in 58 cadavers. *Dis Colon Rectum.* 2002;45(10):1337-40. doi: 10.1097/01.DCR.0000027284.76452.84.
13. Ignjatovic D, Spasojevic M, Stimec B. Can the gastrocolic trunk of Henle serve as an anatomical landmark in laparoscopic right colectomy? A postmortem anatomical study. *Am J Surg.* 2010;199(2):249-54. doi: 10.1016/j.amjsurg.2009.03.010.
14. Stefura T, Kacprzyk A, Droś J, Pędziwiatr M, Major P, Hołda MK. The venous trunk of henle (gastrocolic trunk): A systematic review and meta-analysis of its prevalence, dimensions, and tributary variations. *Clin Anat.* 2018;31(8):1109-1121. doi: 10.1002/ca.23228.
15. Sakaguchi T, Suzuki S, Morita Y, et al. Analysis of anatomic variants of mesenteric veins by 3-dimensional portography using multidetector-row computed tomography. *Am J Surg.* 2010;200(1):15–22. doi: 10.1016/j.amjsurg.2009.05.017.
16. Ogino T, Takemasa I, Horitsugi G, et al. Preoperative evaluation of venous anatomy in laparoscopic complete mesocolic excision for right colon cancer. *Ann Surg Oncol.* 2014;21(Suppl 3):S429-35. doi: 10.1245/s10434-014-3572-2.
17. Japanese Gastric Cancer Association, "Japanese classification of gastric carcinoma: 3rd english edition," *Gastric Cancer.* 2011;14(2):101-12. doi: 10.1007/s10120-011-0041-5.
18. Haruta S, Shinohara H, Ueno M, Udagawa H, Sakai Y, Uyama I. Anatomical considerations of the infrapyloric artery and its associated lymph nodes during laparoscopic gastric cancer surgery. *Gastric Cancer.* 2015;18(4):876–880. doi: 10.1007/s10120-014-0424-5.
19. Methasate A, Trakarnsanga A, Akaraviputh T, Chinsawangwathanakol V, Lohsiriwat D. Lymph node metastasis in gastric cancer: result of D2 dissection. *J Med Assoc Thai.* 2010;93(3):310-7. PMID: 20420105.
20. Han KB, Jang YJ, Kim JH, et al. Clinical significance of the pattern of lymph node metastasis depending on the location of gastric cancer. *J Gastric Cancer.* 2011;11(2):86-93. doi: 10.5230/jgc.2011.11.2.86.
21. Yanzhang W, Guanghua L, Zhihao Z, Zhixiong W, Zhao W. The risk of lymph node metastasis in gastric cancer conforming to indications of endoscopic resection and pylorus-preserving gastrectomy: a single-center retrospective study. *BMC Cancer.* 2021;21(1):1280. doi: 10.1186/s12885-021-09008-8.
22. Cao LL, Huang CM, Lu J, et al. The Impact of Confluence Types of the Right Gastroepiploic Vein on No. 6 Lymphadenectomy During Laparoscopic Radical Gastrectomy. *Medicine (Baltimore).* 2015;94(33):e1383. doi: 10.1097/MD.0000000000001383.
23. Zuo CH, Xie H, Liu J, et al. Characterization of lymph node metastasis and its clinical significance in the surgical treatment of gastric cancer. *Mol Clin Oncol.* 2014;2(5):821–826. doi: 10.3892/mco.2014.303.
24. Deng JY, Liang H. Clinical significance of lymph node metastasis in gastric cancer. *World J Gastroenterol.* 2014;20(14):3967–3975. doi: 10.3748/wjg.v20.i14.3967.
25. Tanizawa Y, Terashima M. Lymph node dissection in the resection of gastric cancer: review of existing evidence. *Gastric Cancer.* 2010;13(3):137–148. doi: 10.1007/s10120-010-0560-5.
26. Maki Y, Mizutani M, Morimoto M, et al. The variations of the middle colic vein tributaries: depiction by three-dimensional CT angiography. *Br J Radiol.* 2016;89(1063):20150841. doi: 10.1259/bjr.20150841.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Punctoplasty surgery combined with 22-gauge intracath intubation in punctal stenosis: A practical, cost-effective, and efficient method

Derya Doganay

University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Ophthalmology, Bursa, Türkiye

ARTICLE INFO

Keywords:
Lacrimal punctum
Nasolacrimal apparatus
Epiphora
Punctal stenosis

Received: Jan 17, 2025
Accepted: Apr 15, 2025
Available Online: 25.04.2025

DOI:
10.5455/annalsmedres.2025.01.022

Abstract

Aim: To evaluate the outcomes of cases with epiphora due to punctal stenosis, in which intubation was performed using a 22-gauge (G) intracath in combination with the two-snip or three-snip technique.

Materials and Methods: The study included 45 eyes of 23 patients with punctal stenosis who presented to our clinic with epiphora. The severity of punctal stenosis in all cases was graded according to the Kashkouli classification; 32 eyes (71.1%) were graded as grade 1, and 13 eyes (28.9%) as grade 2. Epiphora was confirmed using the fluorescein disappearance test. Lacrimal system lavage was performed in all cases to evaluate the distal lacrimal system, and distal passage patency was observed. Cases were considered successful if they had a Munk score of 0 or 1 and a fluorescein disappearance test score of 0.

Results: The study included 10 male and 13 female patients, with a mean age of 62.09 ± 12.41 years. The mean follow-up period was 6.3 ± 4.56 months. Preoperatively, all cases had a Munk score of 4 and a fluorescein disappearance test score of 3. At the final follow-up, no epiphora was observed in 36 eyes (80%), while intermittent epiphora with a Munk score of 2 was reported in 9 eyes (20%). In four eyes with intermittent epiphora, the lavage time exceeded 5 seconds, and in two eyes (one patient), ocular surface disorder due to previous trauma was present. Revision surgery was required in five eyes due to restenosis. Conjunctival reaction developed in six eyes (three patients).

Conclusion: Punctoplasty surgery is an effective option in cases with punctal stenosis. The method we used is effective and cost-efficient in terms of punctal intubation, and it may serve as an alternative to silicone tube intubation.

Introduction

A dysfunction occurring at any point in the lacrimal drainage system clinically presents as epiphora. Punctal stenosis is also a significant cause of epiphora, commonly seen in elderly patients. Although the exact etiology is not fully known, several factors are implicated [1]. These include infections, inflammation, systemic diseases, medications, aging, tumors, and gender. The etiopathogenesis is attributed to fibrosis caused by chronic inflammation [2-6]. Kashkouli et al. classified punctal stenosis based on the morphological findings of stenosis [7,8] (Table 1). In the literature, this classification has no influence on the described treatment approaches. These treatment approaches include dilation, one-snip punctoplasty, two-snip punctoplasty, three-snip punctoplasty, four-snip punctoplasty, Kelly punctal punch, mitomycin C application, punctal plug placement, and silicone intubation [9,10].

The aim of this study is to describe a cost-effective and clinically effective method using a 22-gauge intracath and to present its results.

Materials and Methods

Patients who underwent surgery with 22-gauge intracath intubation due to punctal stenosis after being referred to our oculoplastic unit for complaints of epiphora between January 2020 and June 2024 were included in the study. Approval was obtained from the Clinical Research Ethics Committee of SBÜ Bursa Yuksek Ihtisas Training and Research Hospital (approval date: 13/12/2023; protocol number: 2011-KAEK-25 2023/12-29). Data on patients' demographic characteristics, symptoms, duration

*Corresponding author:
Email address: d3rya1983@gmail.com (Derya Doganay)

Table 1. Kashkouli classification.

Grade	Clinical finding on slit lamp examination
0	No papilla and punctum (punctal atresia)
1	Papilla is covered by a membrane (exudative or true membrane) or fibrosis and difficult to recognize
2	Less than normal size but recognizable
3	Normal
4	Small slit (<2 mm)
5	Large slit (≥2 mm)

of symptoms, previous clinical diagnoses, treatments, and long-term outcomes were evaluated retrospectively. During the diagnostic process, a 2% fluorescein disappearance test was performed on all patients, and distal lacrimal passage patency was examined. Our exclusion criteria in the study were cases with distal lacrimal passage obstruction detected by lavage examination and cases with epiphora due to dry eye. The severity of punctal stenosis in all cases was graded according to the Kashkouli classification.

Postoperative success was defined as a Munk score of 0 or 1 and a fluorescein disappearance test score of 0 (Table 2). All patients underwent either two-snip or three-snip punctoplasty, followed by intubation using a 22-gauge intracath. During intubation, fluid was passed through the intracath to ensure that it remained within the canal without creating an extra passage. The intracath was fixed to the skin with 6/0 vicryl sutures, and intubation was maintained for 7 to 12 days, depending on patient tolerance (Figure 1).

Table 2. Munk scoring.

Grade	Clinical finding
0	No epiphora
1	Epiphora that requires wiping less than twice a day
2	Epiphora requiring 2 to 4 wipings per day
3	Epiphora requiring 5 to 10 wipings per day
4	Epiphora requiring more than ten wipings per day

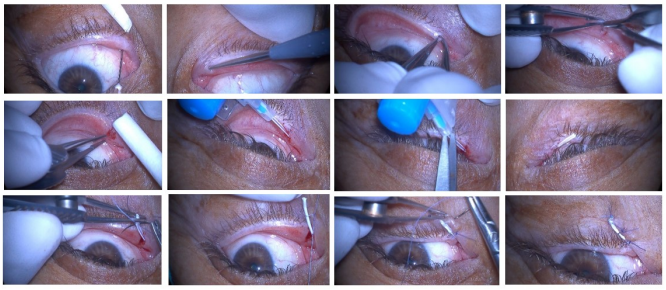

Figure 1. Procedures applied in order from top left to right. Local application of epinephrine-lidocaine HCL (jetocaine) to the surgical site, punctum dilation, application of three-snip punctoplasty, placement of a 22 G intravenous catheter, and skin-intracatheter suturing with 6-0 vicryl sutures.

To assess the normality of the patient data, the Shapiro-Wilk test was conducted, yielding a p-value of 0.3645. This result indicates that the data conform to a normal distribution. Therefore, continuous variables are summarized as mean and standard deviation (mean ± SD), while categorical variables are presented as counts and percentages.

Results

The study included 45 eyes of 23 patients who underwent surgery with 22-gauge intracath intubation due to punctal stenosis. Ten (43.48%) of the patients were male, and 13 (56.52%) were female, with a mean age of 62.09 ± 12.42 years (range: 36-86). The mean follow-up period was 6.30 ± 4.56 months (range: 1-13 months). Preoperatively, all cases had a Munk score of 4 and a fluorescein disappearance test score of 3. The degree of punctal stenosis in all cases was classified according to the Kashkouli classification. According to this classification, 32 eyes (71.1%) were graded as grade 1, and 13 eyes (28.89%) were graded as grade 2. At the final follow-up, no epiphora was observed in 36 eyes (80%), while intermittent epiphora with a Munk score of 2 was reported in 9 eyes (20%). In 4 eyes (9.3%) with intermittent epiphora, the lavage time exceeded 5 seconds and was considered as partial distal lacrimal passage insufficiency. Two eyes (1 patient) had ocular surface disorder due to previous trauma, and the persistence of epiphora was associated with this ocular surface disorder. Postoperatively, 5 eyes (11.63%) developed restenosis, requiring revision surgery. After revision surgery, epiphora was no longer observed. Six eyes (three patients) developed conjunctival reactions in the early postoperative period. This was considered a surgical-related reaction, and corticosteroid drops were applied at a dose of 4 times a day for 4 weeks. No change was observed in the reaction, and to benefit from its anti-inflammatory effect, the treatment was switched to cyclosporine. After cyclosporine application, a rapid clinical response was observed, and the reaction regressed.

Discussion

Punctal stenosis has been found to occur equally in the upper and lower puncta in some studies [11], while in a study by Kashkouli et al., it was localized in the lower punctum in 89.7% of cases [8]. In our study, stenosis was also localized in the lower punctum in all cases.

Although there is no significant difference in punctal stenosis incidence between genders, several studies suggest that it is more common in women, especially as age increases [1,8,12]. Our findings are consistent with the literature.

Various methods have been described for the treatment of punctal stenosis. These treatment methods generally include dilation using a simple dilator, more invasive techniques such as one-snip, two-snip, three-snip, and four-snip punctoplasty, punctoplasty performed with a punch, and various devices used to maintain the patency of the surgically enlarged punctum. Devices such as punctal plugs, mini-monoka stents, self-retaining bicanalicular intubation sets, FCI Nunchaku silicone tubes, and Kaneka Lacrimal silicone sets are used for this purpose.

According to Kashkouli, in cases of stage 2 punctal stenosis, repeated simple dilation methods may be tried. However, repeated dilations will stimulate fibrosis, and iatrogenic stenosis will increase in the long term.

Functional success rates of 92% have been reported with the Reiss punctal punch method [13]. Later developments of the Kelly punch are thought to allow more controlled ampulla resection and cause less damage to the Riolan muscle [14].

In the literature, snip punctoplasty (SP) techniques and their modifications, ranging from one to four snips, have been described. This technique is the oldest and most frequently used method. In a study by Chak and Irvine, they used the 3-SP technique and found a success rate of 89.8% [15]. In another study by Ali et al., they used the 3-SP method and reported a success rate of 74.7%. In a group of 10.3%, anatomical success was achieved, but epiphora persisted [16]. Kim et al. found a success rate of 93.3% in their patient group using the 4-SP technique [17]. In our study, the rate of patients whose epiphora complaints completely resolved was found to be 80%. In 4 eyes (9.3% of patients), the distal passage lavage transition time was longer than 5 seconds, which was evaluated as partial lacrimal passage insufficiency.

In a study by Ali et al., restenosis developed in 5.7% of patients [16]. In our study, restenosis developed in 5 patients (11.68%). The stenosis was reopened with repeated surgical intervention, and during follow-up, the punctum remained patent.

After punctoplasty, intubation materials placed in the punctum can be used to prevent the re-adhesion of the wound lips. In the early stages, after performing punctoplasty with the punch method, silicone punctal plugs were used. However, due to inflammation caused by the silicone material itself, the use of more hydrophilic materials (such as Polyvinylpyrrolidone - PVP) has been adopted [18,19]. Studies have shown that punctoplasty surgery performed with intubation using perforated punctal plugs coated with PVP hydrophilic material yields better results [19].

Intracath tubes, commonly used as intravenous catheters, are frequently made of Teflon by manufacturers. In recent years, Vialon biomaterial has also been preferred. Teflon is a fluoropolymer made of polytetrafluoroethylene (PTFE) [20]. Vialon, on the other hand, is made of polyether urethane and is more flexible, softer, microtextured, and hydrophilic compared to Teflon [21]. The intracath used in this study is made of Teflon (B-cat2 I.V. cannula, intra-cath-2 I.V. cannula) and has a hydrophobic character. However, no studies comparing silicone material and Teflon material have been found in the literature. This could be further supported by future studies.

Mini Monoka (MM) tube implantation can also be performed after punctoplasty surgery. In a study by Hussain et al., they performed intubation with the MM tube for 6 weeks after probing and reported early success rates of 88% [22]. After the use of the MM tube, complications such as tube migration, early extrusion, and tube loss can occur [7]. In this study, the intracath used after intubation is sutured to the skin with 6/0 Vicryl. This helps prevent complications such as dislodgement and migration. Additionally, contact of the rigid tube material with the ocular surface can be avoided. Furthermore, during surgery, fluid is passed through the intracath to confirm that intubation within the canaliculus is performed peroperatively.

The limitations of our study include the absence of a control group for comparison and the lack of literature comparing Teflon and silicone materials, highlighting the need for further studies to support our findings.

Conclusion

In conclusion, we believe that punctoplasty surgery with the aid of a 22G intracath could be a reliable and low-cost alternative method.

Disclosures

Ethics Committee Approval: Ethical approval for this study was obtained from the Clinical Research Ethics Committee of SBU Bursa Yüksek İhtisas Training and Research Hospital (approval date: 13/12/2023; protocol number: 2011-KAEK-25 2023/12-29).

Informed Consent: Not necessary for this manuscript.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Not necessary for this manuscript.

Financial Disclosure: None.

References

1. Viso E, Rodríguez-Ares MT, Gude F. Prevalence and associations of external punctal stenosis in a general population in Spain. *Cornea.* 2012;31(11):1240-5. doi: 10.1097/ICO.0b013e31823f8eca.
2. Port AD, Chen YT, Lelli GJ Jr. Histopathologic changes in punctal stenosis. *Ophthalmic Plast Reconstr Surg.* 2013;29(3):201-4. doi: 10.1097/IOP.0b013e31828a92b0.
3. Jager GV, Van Bijsterveld OP. Canalicular stenosis in the course of primary herpes simplex infection. *Br J Ophthalmol.* 1997;81(4):332. doi: 10.1136/bjo.81.4.329d.
4. McNab AA. Lacrimal canalicular obstruction associated with topical ocular medication. *Aust N Z J Ophthalmol.* 1998;26(3):219-23. doi: 10.1111/j.1442-9071.1998.tb01315.x.
5. Rumelt S, Pe'er J, Rubin PA. The clinicopathological spectrum of benign peripunctal tumours. *Graefes Arch Clin Exp Ophthalmol.* 2005;243(2):113-119. doi: 10.1007/s00417-004-0907-x.
6. Matta CS, Felker GV, Ide CH. Eye manifestations in acrodermatitis enteropathica. *Arch Ophthalmol.* 1975;93(2):140-42. doi: 10.1001/archopht.1975.01010020146012.
7. Kashkouli MB, Beigi B, Astbury N. Acquired external punctal stenosis: Surgical management and long-term follow up. *Orbit.* 2005;24(2):73-78. doi: 10.1080/01676830490916055.
8. Kashkouli MB, Beigi B, Murthy R, Astbury N. Acquired external punctal stenosis: Etiology and associated findings. *Am J Ophthalmol.* 2003;136(6):1079-84. doi: 10.1016/s0002-9394(03)00664-0.
9. Caesar RH, McNab AA. A brief history of punctoplasty: The three snips revisited. *Eye.* 2005;19(1):16-18. doi: 10.1038/sj.eye.6701415.
10. Mathew RG, Olver JM. Mini-monoka made easy: A simple technique for mini-monoka insertion in acquired punctal stenosis. *Ophthal Plast Reconstr Surg.* 2011;27(4):293-94. doi: 10.1097/IOP.0b013e31820ccfaf.
11. Bukhari A. Prevalence of punctal stenosis among ophthalmology patients. *Middle East Afr J Ophthalmol.* 2009;16(2):85-87. doi: 10.4103/0974-9233.53867.
12. Offutt WN, Cowen DE. Stenotic puncta: microsurgical punctoplasty. *Ophthalm Plast Reconstr Surg.* 1993;9(3):201-5. doi: 10.1097/00002341-199309000-00006.
13. Edelstein J, Reiss G. The wedge punctoplasty for treatment of punctal stenosis. *Ophthalmic Surg.* 1992;23(12):818-21. PMID: 1494436.
14. Priel A, Rosner M, Ben Simon G, Weidenfeld J, Weissman A, Prat D, Zloto O. The clinical and histopathological characteristics of Kelly punch punctoplasty. *Eye (Lond).* 2020;34(12):2295-99. doi: 10.1038/s41433-020-0813-4.

15. Chak M, Irvine F. Rectangular 3-snip punctoplasty outcomes: preservation of the lacrimal pump in punctoplasty surgery. *Ophthalmic Plast Reconstr Surg.* 2009;25(2):134-135. doi: 10.1097/IOP.0b013e3181994062.
16. Ali MJ, Ayyar A, Naik MN. Outcomes of rectangular 3-snip punctoplasty in acquired punctal stenosis: is there a need to be minimally invasive? *Eye (Lond).* 2015;29(4):515-8. doi: 10.1038/eye.2014.342.
17. Kim SE, Lee SJ, Lee SY, Yoon JS. Outcomes of 4-snip punctoplasty for severe punctal stenosis: measurement of tear meniscus height by optical coherence tomography. *Am J Ophthalmol.* 2012;153(4):769-73. doi: 10.1016/j.ajo.2011.09.026.
18. Msallam MM. Bilateral simultaneous pyogenic granuloma after perforated punctal plug insertion. *Ophthalmic Plast Reconstr Surg.* 2014;30(5):e113-15. doi: 10.1097/IOP.0b013e3182a5ba6b.
19. Konuk O, Urgancioglu B, Unal M. Long-term success rate of perforated punctal plugs in the management of acquired punctal stenosis. *Ophthalmic Plast Reconstr Surg.* 2008;24(5):399-402. doi: 10.1097/IOP.0b013e318185a9ca.
20. Chhugani M, James MM, Thokchom S. A Randomized Controlled Trial to Assess the Effectiveness of Vialon™ Cannula Versus Polytetrafluoroethylene (PTFE) Cannula in Terms of Indwelling Time and Complications in Patients Requiring Peripheral Intravenous Cannulation. *International Journal of Science and Research (IJSR).* 2015;4(12):1075-80.
21. O'Grady NP, Alexander M, Burns LA, et al. Healthcare Infection Control Practices Advisory Committee. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control.* 2011;39(4 Suppl 1):S1-34. doi: 10.1016/j.ajic.2011.01.003.
22. Hussain RN, Kanani H, McMullan T. Use of mini monoka stents for punctal/canalicular stenosis. *Br J Ophthalmol.* 2012;96(5):671-73. doi: 10.1136/bjophthalmol-2011-300670.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Danger-associated molecular patterns and their effects in graft-versus-host disease

Derya Koyun

Bitlis Tatvan State Hospital, Department of Hematology, Bitlis, Türkiye

ARTICLE INFO

Received: Jan 06, 2025
Accepted: Jan 15, 2025
Available Online: 25.04.2025

DOI:
10.5455/annalsmedres.2025.01.06

Dear Editor,

Hematopoietic stem cell transplantation continues to be the gold standard treatment option for various blood cancers, and one of its mortal complications is graft-versus-host disease (GVHD). This is due to cell death as a result of tissue damage following chemotherapy and/or radiotherapy during the preparation for transplantation. It is also known that danger-associated molecules liberated during tissue damage after chemotherapy and radiotherapy may be responsible for the development of GVHD. Endogenous and exogenous pathogen-associated molecular patterns trigger a potent danger signal response and it is defined as damage-associated molecular patterns. These danger signals result in cytokine release by activating nuclear transcription factors such as nuclear factor (NF)-κB, early growth response factor (Egr1), and activator protein (AP)-1. These are classified into exogenous and endogenous factors. Endogenous danger-associated molecular patterns include factors such as high mobility group box 1 (HMGB-1), S100 proteins, elastase inhibitors, defensins, cathelicidins, regenerative protein family (Reg), heat shock proteins, heparan sulfate proteoglycans, adenosine triphosphate, and uric acid and induce danger signals almost immediately during unprogrammed cell death [1]. New therapeutic option targeting danger-associated molecular patterns may be a promising alternative for GVHD therapy.

Heparan sulfate is a complex, linear polysaccharide belonging to the glycosaminoglycan familythat shows a diverse interaction with intracellular and extracellular matrices. At the beginning of GVHD, the serum concentration of heparan sulfate rises and correlates with the disease's severity. Studies on experimental models have shown that alpha-1 antitrypsinsignificantly lowers heparan sulfate levels, and this decrease in heparan sulfate is linked to a decrease in the intensity of GVHD. Moreover, alpha-1 antitrypsin reduces inflammatory cytokines like TNF-α and IL-1β. However, it boosts IL-10 production, and promotes Treg expansion [2]. In our center, we also demonstrated that alpha-1 antitrypsin, which affects heparan sulfate levels, plays an important role in resistance to acute GVHD after allogeneic stem cell transplantation in 5 patients [3]. No treatment-related side effects were observed in our patients included. Further studies on different danger-associated molecular patterns, and their efficacy in the treatment of GVHD should be panned.

References

1. Ramadan A, Paczesny S. Various forms of tissue damage and danger signals following hematopoietic stem-cell transplantation. *Front Immunol.* 2015;6:14. doi: 10.3389/fimmu.2015.00014.
2. Tawara I, Sun Y, Lewis EC, Toubai T, Eversa R, Nieves E, AzamT, Dinarello CA, Reddy. Alpha-1-antitrypsin monotherapy reduces graft-versus-host disease after experimental allogeneic bone marrow transplantation. *Proc Natl Acad Sci USA.* 2011:109(2):564–569. doi: 10.1073/pnas.1117665109.

*Corresponding author:
Email address: deryakoyun11@gmail.com (Derya Koyun)

3. Koyun D, et al. Alpha-1-Antitrypsin Experience for Steroid-Resistant Acute Graft-Versus-Host Disease. *Indian Journal of Hematology and Blood Transfusion.* 2022;38(3):601-605. doi: 10.1007/s12288-022-01524-2.